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(71) Applicant *(for all designated States except US)*: FUJISAWA PHARMACEUTICAL CO., LTD. [JP/JP]; 4-7, Doshomachi 3-chome, Chuo-ku, Osaka-shi, Osaka 541 (JP).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: KAWAI, Yoshio [JP/JP]; 3-33-14, Kamikashiwada, Ushiku-shi, Ibaraki 300-12 (JP). SATOH, Shigeki [JP/JP]; 3-25-4-304, Matsushiro, Tsukuba-shi, Ibaraki 305 (JP). YAMAZAKI, Hitoshi [JP/JP]; 4-3-4, Matsushiro, Tsukuba-shi, Ibaraki 305 (JP). KAYAKIRI, Natsuko [JP/JP]; 2-31-15, Umezono, Tsukuba-shi, Ibaraki 305 (JP). YOSHIHARA, Kousei [JP/JP]; 2-1-21-103, Higashi, Toride-shi, Ibaraki 302 (JP). OKU, Teruo [JP/JP]; 8-2, Midorigaoka, Tsukuba-shi, Ibaraki 305 (JP).

(74) Agent: SEKI, Hideo; Fujisawa Pharmaceutical Co., Ltd., Osaka Factory, 1-6, Kashima 2-chome, Yodogawa-ku, Osaka-shi, Osaka 532 (JP).

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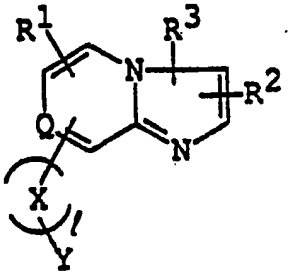
(54) Title: IMIDAZO 1,2-A PYRIDINE AND IMIDAZO 1,2-A PYRIDEZINE DERIVATIVES AND THEIR USE AS BONE RESORPTION INHIBITORS



(I)

$-NHCO-$, $-NHSO_2-$, $-OCO-$, $-OCH_2-$, $-NHCOCO-$, $-NHCOCH=CH-$, $-NHCOCH_2-$, $-NHCONH-$ or $-N(R^5)-CO-$ (a)

(57) Abstract

This invention relates to a novel imidazopyridine compound represented by formula (I), wherein X is vinylene, or a group of the formula (a), Y is heterocyclic group which may have one or more suitable substituent(s), or aryl which may have one or more suitable substituent(s), Q is CH or N, and l is an integer of 0 or 1, which are the inhibitors of bone resorption and bone metabolism, to processes for preparation thereof, to a pharmaceutical composition comprising the same and to a method for the treatment of diseases caused by abnormal bone metabolism in human being or an animal.

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DESCRIPTION

IMIDAZO 1,2-A PYRIDINE AND IMIDAZO 1,2-A PYRIDEZINE DERIVATIVES AND THEIR USE AS BONE RESORPTION INHIBITORS

TECHNICAL FIELD

The present invention relates to a novel imidazopyridine or imidazopyrazine (hereinafter referred to as "imidazopyridine") compound and a pharmaceutically acceptable salt thereof which are useful as a medicament.

BACKGROUND ART

In Japanese Patent Application Laid-open No.60-48924, No. 60-54379, etc., there are disclosed thionaphten-2-carboxylic acid derivatives and 3-phenyl-4H-1-benzopyran-4-one derivatives inhibiting bone resorption.

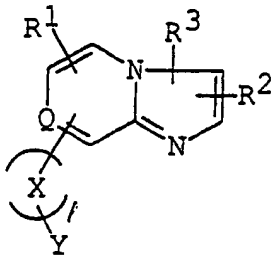
DISCLOSURE OF INVENTION

The present invention relates to a novel imidazopyridine compound and a pharmaceutically acceptable salt thereof which are the inhibitors of bone resorption, the inhibitors of bone metastases and useful for the prophylactic and/or therapeutic treatment of bone disease characterized by abnormal bone metabolism such as osteoporosis (especially, postmenopausal osteoporosis); hyper-calcemia; hyperparathyroidism; Paget's bone diseases; osteolysis; hypercalcemia of malignancy with or without bone metastases; rheumatoid arthritis; periodontitis; osteoarthritis; ostealgia; osteopenia; cancer cachexia; calculosis; lithiasis (especially, urolithiasis); or the like in a human being or an animal.

And further, the present invention relates to processes for the preparation of the imidazopyridine derivatives, to a pharmaceutical composition comprising the same and to a method for the prophylactic and/or therapeutic treatment of above-mentioned diseases in a human being or an animal, and to a use of the imidazopyridine compound and pharmaceutically

acceptable salts thereof for the prophylactic and/or therapeutic treatment of above-mentioned diseases in human being or an animal.

The imidazopyridine compounds of this invention are new and can be represented by the following general formula (I) :



(I)

wherein

R^1 is hydrogen, lower alkyl, an acyl group, amino, acylamino, nitro, halogen or hydroxy(lower)alkyl which may have one or more suitable substituent(s),

R^2 is hydrogen, lower alkyl, an acyl group, lower alkoxy, acyl(lower)alkyl, aryl, cyano, mono-(or di- or tri-)-halo(lower)alkyl, lower alkylthio or hydroxy(lower)alkyl which may have one or more suitable substituent(s),

R^3 is hydrogen, lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy, cyclo(lower)alkyl(lower)alkyl, halogen, an acyl group, acyl(lower)alkyl, acylamino, acylamino(lower)alkyl, acyl(lower)alkenyl, acyloxy(lower)alkyl, acyl(lower)alkylthio(lower)alkyl, amino(lower)alkyl, mono-(or di-)lower alkylamino, lower alkylthio(lower)alkyl, hydroxyimino(lower)alkyl which may have one or more suitable substituent(s), hydroxy(lower)alkyl which may have one or more suitable substituent(s), hydroxy(lower)alkylthio(lower)alkyl, cyano(lower)alkyl, mono-(or di-)lower alkoxy(lower)alkyl

which may have one or more suitable substituent(s), lower alkyl substituted with aryl which may have one or more suitable substituent(s), mono-(or di-)lower alkylamino(lower)alkyl, tri(lower)alkylammonio(lower)-alkyl, lower alkyl substituted with heterocyclic group which may have one or more suitable substituent(s), hydrazino(lower)alkyl which may have one or more suitable substituent(s), mono- or di-(lower)alkoxy(lower)alkylamino(lower)alkyl, (lower)alkylamino(lower)alkyl which may have one or more suitable substituent(s), heterocyclic group which may have one or more suitable substituent(s), heterocyclicthio, heterocyclicthio(lower)alkyl which may have one or more suitable substituent(s), heterocyclicoxy, heterocyclicoxy(lower)alkyl, heterocyclicaminoimino(lower)alkyl, aryl which may have one or more suitable substituent(s), amino, nitro, halo(lower)alkyl, hydroxy(lower)alkylimino(lower)alkyl, hydroxy(lower)alkylamino(lower)alkyl, bis-[hydroxy(lower)alkyl]amino(lower)alkyl, mercapto(lower)alkyl or amidinothio(lower)alkyl,

in which R^2 and R^3 may be linked together to form

(1) lower alkylene which may have one or more suitable substituent(s),

(2) lower alkenylene which may have one or more suitable substituent(s), or

(3) a group of the formula :

$$-(A^1)_m-W-(A^2)_n-$$

[wherein A^1 and A^2 are each lower alkylene which may have one or more suitable substituent(s) or lower

alkenylene which may have one or more suitable substituent(s),

W is -S-, $-\overset{\overset{O}{\|}}{S}-$, or $-\overset{\overset{R^4}{|}}{N}-$ (wherein R^4 is hydrogen, lower alkyl or an acyl group)

and

m and n are each an integer of 0 or 1],

X is vinylene, or a group of the formula :

$-NHCO-$, $-NHSO_2-$, $-OCO-$, $-OCH_2-$, $-NHCOCO-$, $-NHCOCH=CH-$, $-NHCOCH_2-$, $-NHCONH-$ or $-\overset{\overset{R^5}{|}}{N}-CO-$

(wherein R^5 is lower alkyl),

Y is heterocyclic group which may have one or more suitable substituent(s), or aryl which may have one or more suitable substituent(s),

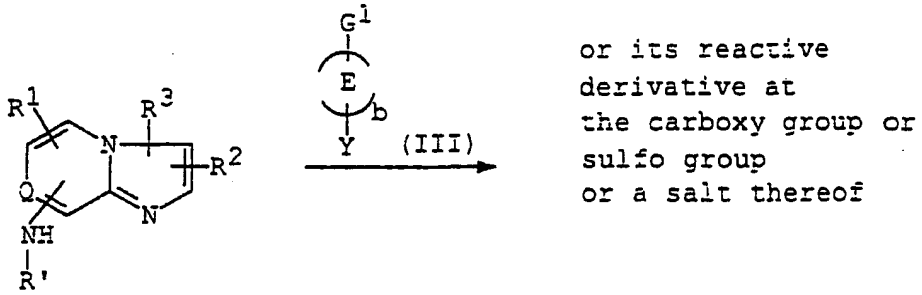
Q is CH or N, and

ℓ is an integer of 0 or 1,

and a pharmaceutically acceptable salt thereof.

The object compound (I) or a salt thereof can be prepared by the processes as illustrated in the following reaction schemes.

Process 1

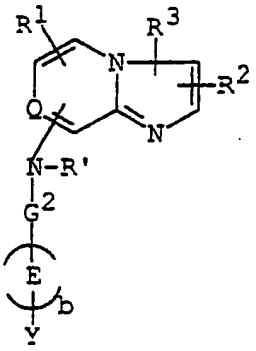


(II)

or its reactive derivative at the amino group or a salt thereof

(III)

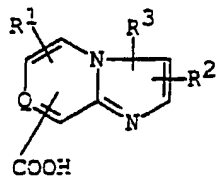
or its reactive derivative at the carboxy group or sulfo group or a salt thereof



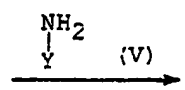
(Ia)

or a salt thereof

Process 2

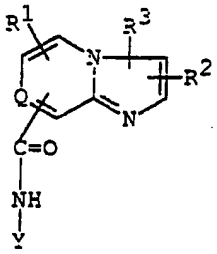


(IV)
or its reactive derivative at the carboxy group or a salt thereof



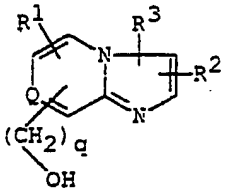
(V)

or its reactive derivative at the amino group or a salt thereof

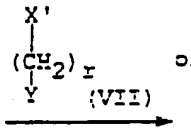


(Ib)
or a salt thereof

Process 3

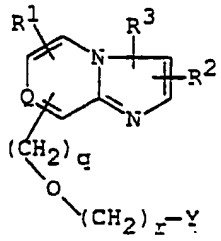


(VI)
or its reactive derivative at the hydroxy group or a salt thereof



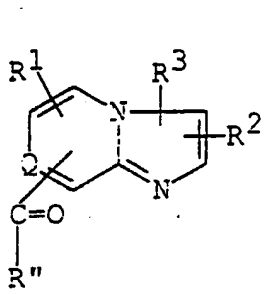
(VII)

or a salt thereof

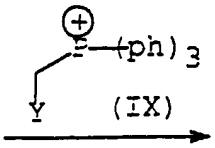


(Ic)
or a salt thereof

Process 4

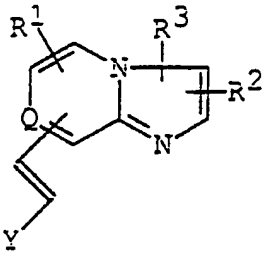


(VIII)
or a salt thereof



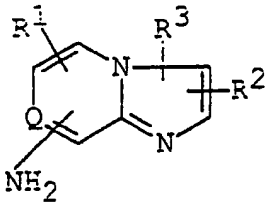
(IX)

or salt thereof



(Id)
or a salt thereof

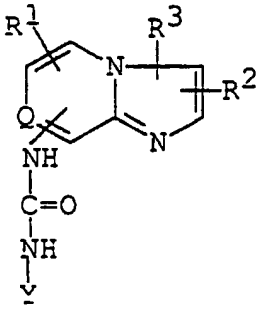
Process 5



(X)
or its reactive derivative at the amino group
or a salt thereof

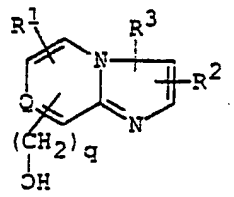
Y-N=C=O
(XI)

or a salt thereof



(Ie)
or a salt thereof

Process 6



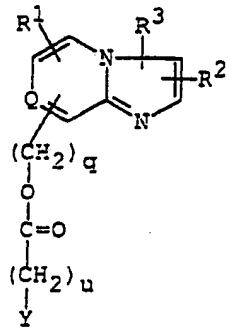
(VI)

or its reactive derivative at the hydroxy group or a salt thereof

$Y-(CH_2)_u-COOH$

(XII)

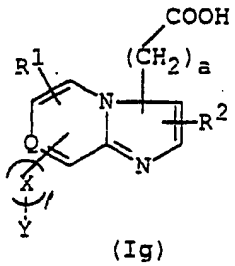
or its reactive derivative at the carboxy group or a salt thereof



(If)

or a salt thereof

Process 7



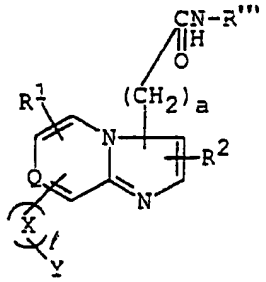
(Ig)

or its reactive derivative at the carboxy group or a salt thereof

NH_2-R'''

(XIII)

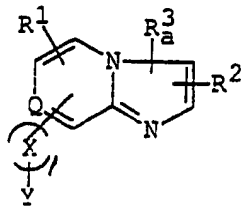
or its reactive derivative at the amino group or a salt thereof



(Ih)

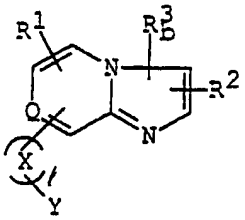
or a salt thereof

Process 8



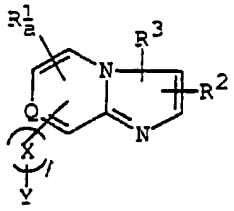
(Ii)
or a salt thereof

Grignard reagent



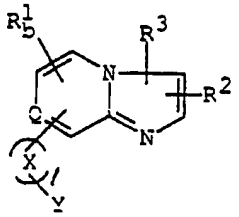
(Ij)
or a salt thereof

Process 9



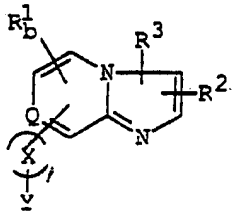
(Ik)
or a salt thereof

de-acylation



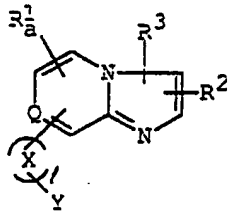
(Il)
or a salt thereof

Process 10



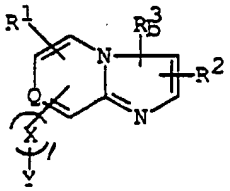
(I l)
or a salt thereof

acylation



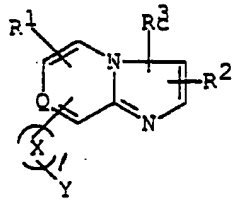
(Ik)
or a salt thereof

Process 11



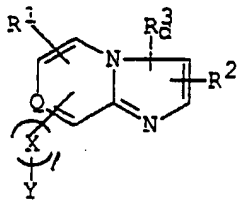
(Ij)
or a salt thereof

acylation



(Im)
or a salt thereof

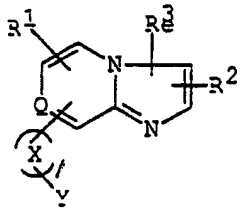
Process 12



(In)
or a salt thereof

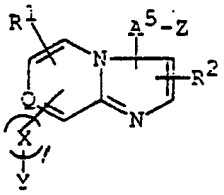
lower alkane substituted with oxo or a salt thereof

(XIV)



(Io)
or a salt thereof

Process 13

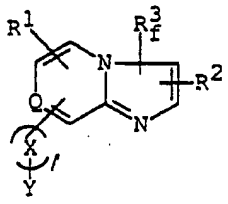


(Ip)
or a salt thereof

V - H

(XV)

or a salt thereof



(Iq)
or a salt thereof

wherein

R^1, R^2, R^3, X, Y, Q and ℓ are each as defined above,

R^1_a is acylamino,

R^1_b is amino,

R^3_a is lower alkyl substituted with oxo,

R^3_b is hydroxy(lower)alkyl,

R^3_c is acyloxy(lower)alkyl,

R^3_d is hydrogen,

R^3_e is hydroxy(lower)alkyl,

R^3_f is lower alkyl substituted with heterocyclic group which may have one or more suitable substituent(s), heterocyclicthio(lower)alkyl, lower alkylamino(lower)alkyl which may have one or more suitable substituent(s), hydroxy(lower)alkylamino(lower)alkyl, bis-[hydroxy(lower)alkyl]amino(lower)alkyl, amidinothio(lower)alkyl or di-(lower)alkoxyphosphoryl(lower)alkyl,

E is lower alkylene, lower alkenylene or a group of the formula :

,

V is heterocyclic group which may have one or more suitable substituent(s), heterocyclicthio, or lower alkylamino which may have one or more suitable substituent(s), hydroxy(lower)alkylamino, bis-hydroxy(lower)alkylamino, amidinothio or tri-lower alkylphosphite,

Z is leaving group,

A^5 is lower alkylene,

R' is hydrogen or lower alkyl,

R" is leaving group,

R"' is lower alkyl, cyclo(lower)alkyl, lower alkyl substituted with heterocyclic group which may have one or more suitable substituent(s), lower

alkoxy(lower)alkyl, hydroxy(lower)alkyl, amino, heterocyclic group, carboxy(lower)alkyl, protected carboxy(lower)alkyl, lower alkyl substituted with aryl which may have one or more suitable substituent(s) or arylsulfonyl or cyano(lower)alkyl,

G^1 is -COOH or $-SO_3H$,

G^2 is -CO- or $-SO_2-$,

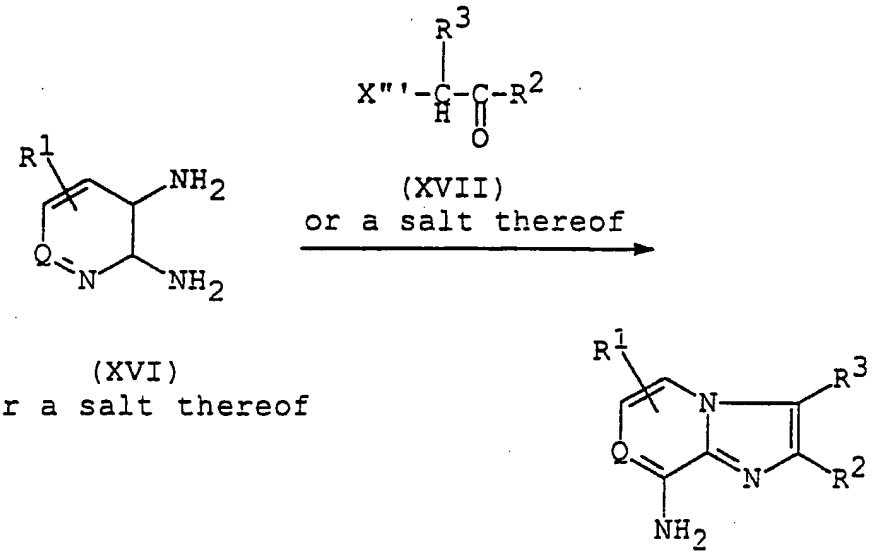
X' is halogen,

a is an integer of 0 to 6, and

b, r, q and u are each an integer of 0 or 1.

Some of the Starting compound (II) or a salt thereof is novel and can be prepared by the following schemes.

Process A



wherein R^1, R^2, R^3 and Q are each as defined above, and
X"' is halogen.

Suitable pharmaceutically acceptable salts of the object compound (I) are conventional non-toxic salts and may include a salt with a base or an acid addition salt such as a salt with an inorganic base, for example, an alkali metal salt (e.g., sodium salt, potassium salt, etc.), an alkaline earth metal salt (e.g., calcium salt, magnesium salt, etc.), an ammonium salt; a salt with an organic base, for example, an organic amine salt (e.g., triethylamine salt, pyridine salt, picoline salt, ethanolamine salt, triethanolamine salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt, etc.); an inorganic acid addition salt (e.g., hydrochloride, hydrobromide, sulfate, phosphate, etc.); an organic carboxylic or sulfonic acid addition salt (e.g., formate, acetate, trifluoroacetate, maleate, tartrate, fumarate, methanesulfonate, benzenesulfonate, toluenesulfonate, etc.); a salt with a basic or acidic amino acid (e.g., arginine, aspartic acid, glutamic acid, etc.).

In the above and subsequent descriptions of the present specification, suitable examples and illustration of the various definitions which the present invention intends to include within the scope thereof are explained in detail as follows.

The term "lower" is used to intend a group having 1 to 6 carbon atom(s), unless otherwise provided.

The term "higher" is used to intend a group having 7 to 20 carbon atoms, unless otherwise provided.

Suitable example of "one or more" may be the number of 1 to 6, in which the preferred one may be the number of 1 to 4.

Suitable "lower alkyl" and "lower alkyl moiety" may include straight or branched one having 1 to 6 carbon

atom(s), such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, 3-pentyl, isopentyl, tert-pentyl, neopentyl, hexyl, isohexyl, and the like, preferably one having 1 to 5 carbon atom(s).

Suitable "lower alkane" may include straight or branched one having 1 to 6 carbon atom(s), such as methane, ethane, propane, isopropane, butane, isobutane, sec-butane, tert-butane, pentane, 3-pentane, isopentane, tert-pentane, neopentane, hexane, isohexane, and the like, i nwhich the more preferred one may be (C_1-C_4)alkane, and the most preferred one may be methane.

Suitable "lower alkenyl" and "lower alkenyl moiety" may include vinyl, 1-(or 2-)propenyl, 1-(or 2- or 3-)butenyl, 1-(or 2- or 3- or 4-)pentenyl, 1-(or 2- or 3- or 4- or 5-)-hexenyl, methylvinyl, ethylvinyl, 1-(or 2- or 3-)methyl-1-(or 2-)propenyl, 1-(or 2- or 3-)ethyl-1-(or 2-)propenyl, 1-(or 2- or 3- or 4-)methyl-1-(or 2- or 3-)butenyl, and the like, in which more preferable example may be (C_2-C_4)alkenyl, and the most preferred one may be methylvinyl.

Suitable "lower alkynyl" may include ethynyl, 1-propynyl, propargyl, 1-methylpropargyl, 1-(or 2- or 3-)-butynyl, 1-(or 2- or 3- or 4-)pentynyl, 1-(or 2- or 3- or 4- or 5-)hexynyl, and the like, in which more preferable example may be (C_2-C_4)alkynyl, and the most preferred one may be ethynyl.

Suitable "lower alkoxy" may include methoxy, ethoxy, propoxy isopropoxy, butoxy, isobutoxy, t-butoxy, pentyloxy, t-pentyloxy, hexyloxy and the like.

Suitable "aryl" and "aryl moiety" may include phenyl, naphthyl, anthryl and the like.

Suitable "leaving group" may include acid residue, "tri(lower)alkylammonio" as defined below and the like, and suitable examples of "acid residue" may be halogen (e.g., fluorine, chlorine, bromine, iodine.), acyloxy [e.g., sulfonyloxy (e.g., phenylsulfonyloxy, tosyloxy, mesyloxy,

etc.), lower alkanoyloxy (e.g., acetyloxy, propionyloxy, etc.), etc.}, lower alkyl (e.g., methyl, ethyl propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, neopentyl, t-pentyl, hexyl, etc.), aryl (e.g., phenyl, naphthyl, anthryl, etc.), ar(lower)alkyl such as phenyl(lower)alkyl (e.g., benzyl, phenethyl, phenylpropyl, etc.), di(lower)alkylamino (e.g., dimethylamino, diethylamino, diisopropylamino, ethylmethylamino, isopropylmethylamino, ethylmethylamino, ethylpropylamino, etc.), lower alkyl(lower)alkoxyamino(e.g., methylmethoxyamino, methylethylamino, ethylmethoxyamino, ethylethoxyamino, etc.) or the like.

The preferred examples of "tri(lower)alkylammonio" may be trimethylammonio, triethylammonio, tripropylammonio, tributylammonio, tripentylammonio, trihexylammonio, or the like, in which the preferred one may be tri(C_1-C_4)-alkylammonio, and the most preferred one may be trimethylammonio.

Suitable "acid residue" may include halogen (e.g., fluorine chlorine, bromine, iodine, etc.), acyloxy [e.g., sulfonyloxy (e.g., phenylsulfonyloxy, tosyloxy, mesyloxy, etc.), lower alkanoyloxy (e.g., acetyloxy, propionyloxy, etc.), etc.] and the like.

Suitable "lower alkylene" may include straight or branched one such as methylene, ethylene, trimethylene, tetramethylene, pentamethylene, hexamethylene, methylmethylene, ethylethylene, ethylpropylene, and the like.

Suitable "lower alkenylene" may include straight or branched one having 2 to 6 carbon atom(s) such as vinylene, propenylene, 1-(or 2-)butenylene, 1-(or 2- or 3-)pentenylene, 1-(or 2- or 3-)hexenylene, methylvinylene, ethylvinylene, 1-(or 2- or 3-)methylpropenylene, 1-(or 2- or 3-)-ethylpropenylene, 1-(or 2- or 3- or 4-)methyl-1-(or 2-)-butenylene, and the like.

Suitable "cyclo(lower)alkyl" may include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like, in which the preferred one may be cyclo(C_4-C_6)alkyl.

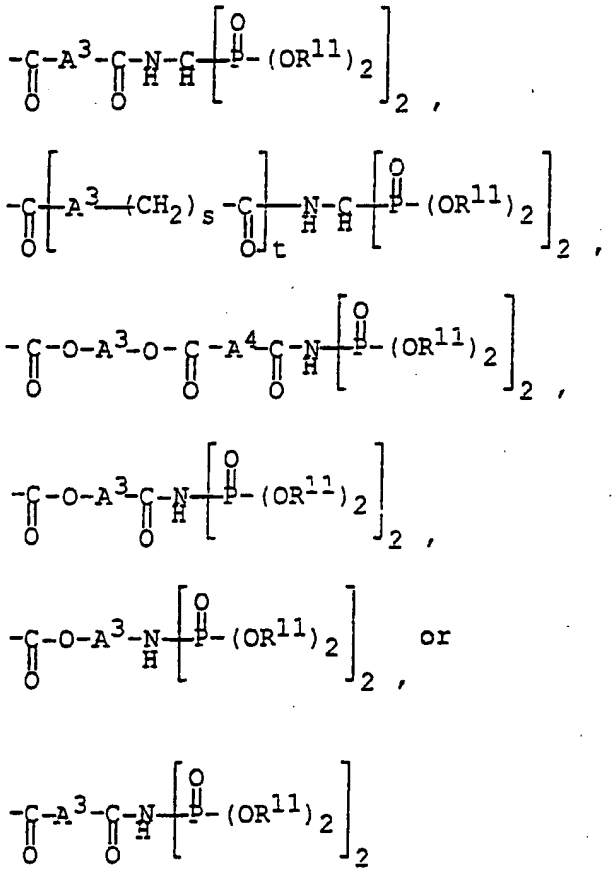
Suitable "halogen" and "halo" moiety may include fluorine, bromine, chlorine, and iodine.

Suitable "an acyl group" and "acyl" moiety may include carbamoyl, aliphatic acyl group and acyl group containing an aromatic ring, which is referred to as aromatic acyl, or heterocyclic ring, which is referred to as heterocyclic acyl.

Suitable example of said acyl may be illustrated as follows :

carbamoyl; carboxy;

aliphatic acyl such as lower or higher alkanoyl (e.g., formyl, acetyl, propanoyl, butanoyl, 2-methylpropanoyl, pentanoyl, 2,2-dimethylpropanoyl, hexanoyl, heptanoyl, octanoyl, nonanoyl, decanoyl, undecanoyl, dodecanoyl, tridecanoyl, tetradecanoyl, pentadecanoyl, hexadecanoyl, heptadecanoyl, octadecanoyl, nonadecanoyl, icosanoyl, etc.); cyclo(lower)alkylcarbonyl (e.g., cyclopropylcarbonyl, cyclobutylcarbonyl, cyclopentylcarbonyl, cyclohexylcarbonyl, etc.); protected carboxy such as commonly protected carboxy [e.g., esterified carboxy such as lower or higher alkoxycarbonyl (e.g., methoxycarbonyl, ethoxycarbonyl, propyloxycarbonyl, iso-propyloxycarbonyl, t-butoxycarbonyl, t-pentyloxycarbonyl, heptyloxycarbonyl, etc.), etc.], or the like; lower or higher alkylsulfonyl (e.g., methylsulfonyl, ethylsulfonyl, etc.); lower or higher alkoxysulfonyl (e.g., methoxysulfonyl, ethoxysulfonyl, etc.); di(lower)alkoxyphosphoryl (e.g., dimethoxyphosphoryl, diethoxyphosphoryl, dipropoxyphosphoryl, dibutoxyphosphoryl, dipentyloxyphosphoryl, dihexyloxyphosphoryl, etc.), a group of the formulas :



(wherein A^3 and A^4 are lower alkylene, amino(lower)alkylene or aminophenylene,
R^{11} is lower alkyl or hydrogen and
S and t are each integer of 1 to 6, or the like);

aromatic acyl such as
aroyl (e.g., benzoyl, toluoyl, naphthoyl, etc.);
ar(lower)alkanoyl [e.g., phenyl(lower)alkanoyl (e.g., phenylacetyl, phenylpropanoyl, phenylbutanoyl, phenylisobutanoyl, phenylpentanoyl, phenylhexanoyl, etc.), naphthyl(lower)alkanoyl (e.g., naphthylacetyl, naphthylpropanoyl, naphthylbutanoyl, etc.), etc.];
ar(lower)alkenoyl [e.g., phenyl(lower)alkenoyl (e.g., phenylpropenoyl, phenylbutenoyl, phenylmethacryloyl, phenylpentenoyl, phenylhexenoyl, etc.), naphthyl(lower)alkenoyl (e.g., naphthylpropenoyl, naphthylbutenoyl, etc.), etc.];
ar(lower)alkoxycarbonyl [e.g., phenyl(lower)alkoxycarbonyl (e.g. benzyloxycarbonyl, etc.), etc.];
aryloxycarbonyl (e.g., phenoxycarbonyl, naphthyloxycarbonyl, etc.);
aryloxy(lower)alkanoyl (e.g., phenoxyacetyl, phenoxypropionyl, etc.);
arylcarbamoyl (e.g., phenylcarbamoyl, etc.);
arylthiocarbamoyl (e.g., phenylthiocarbamoyl, etc.);
arylglyoxyloyl (e.g., phenylglyoxyloyl, naphthylglyoxyloyl, etc.); arylsulfonyl (e.g., phenylsulfonyl, p-tolylsulfonyl, etc.); or the like.

heterocyclic acyl such as
heterocycliccarbonyl;
heterocyclic(lower)alkanoyl (e.g., heterocyclicacetyl, heterocyclicpropanoyl, heterocyclicbutanoyl, heterocyclicpentanoyl, heterocyclichexanoyl, etc.);
heterocyclic(lower)alkenoyl (e.g., heterocyclicpropenoyl, heterocyclicbutenoyl, heterocyclicpentenoyl, heterocyclichexenoyl, etc.); heterocyclicglyoxyloyl; heterocyclicsulfinyl; heterocyclicsulfonyl; or the like; and the like.

Suitable "heterocyclic group" and "heterocyclic moiety"

may include saturated or unsaturated monocyclic or polycyclic heterocyclic group containing at least one hetero-atom such as an oxygen, sulfur, nitrogen atom and the like.

And, especially preferable one may be heterocyclic group such as

unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 4 nitrogen atom(s), for example, pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl, dihydropyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazolyl (e.g., 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, etc.), tetrazolyl (e.g., 1H-tetrazolyl, 2H-tetrazolyl, etc.), etc.;

saturated 3 to 8-membered (more preferably 5 or 6-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s), for example, pyrrolidinyl, imidazolidinyl, piperidyl, piperazinyl, etc.;

unsaturated condensed heterocyclic group containing 1 to 4 nitrogen atom(s), for example, indolyl, isoindolyl, indolinyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, phthalimidyl, etc.;

unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, oxazolyl, isoxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, etc.), etc.;

saturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, morpholinyl, sydnonyl, etc.;

unsaturated condensed heterocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, benzoxazolyl, benzoxadiazolyl, etc.;

unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, thiazolyl,

isothiazolyl, thiadiazolyl (e.g., 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, etc.), dihydrothiazinyl, etc.;

saturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, thiazolidinyl, etc.;

unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 2 sulfur atom(s), for example, thienyl, dihydrodithiinyl, dihydrodithionyl, etc.;

unsaturated condensed heterocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, benzothiazolyl, benzothiadiazolyl, etc.;

unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing an oxygen atom, for example, furyl, pyranyl, etc.;

saturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 2 oxygen atom(s), for example, oxiranyl, oxolanyl, dioxolanyl, tetrahydrofuranyl, etc.;

unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing an oxygen atom and 1 to 2 sulfur atom(s), for example, dihydrooxathiinyl, etc.;

unsaturated condensed heterocyclic group containing 1 to 4 oxygen atom(s), for example, methylenedioxyphenyl, benzodioxanyl, etc.;

unsaturated condensed heterocyclic group containing 1 to 2 sulfur atom(s), for example, benzothienyl, benzodithiinyl, etc.;

unsaturated condensed heterocyclic group containing an oxygen atom and 1 to 2 sulfur atom(s), for example, benzoxathiinyl, etc.; and the like,

and "heterocyclic group" and "heterocyclic moiety" as stated

above may have one or more suitable substituent(s) such as oxo; halogen (e.g., fluorine, chlorine, bromine, iodine, etc.); hydroxy; aforementioned "heterocyclic group"; trihalo(lower)alkyl (e.g., trichloromethyl, trifluoromethyl, trichloroethyl, trifluoroethyl, etc.); lower alkanoyl (e.g., formyl, acetyl, propanoyl, butanoyl, 2-methylpropanoyl, pentanoyl, 2,2-dimethylpropanoyl, hexanoyl, etc.); aryl (e.g., phenyl, naphthyl, anthryl, etc.); lower alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, 3-pentyl, isopentyl, tert-pentyl, neopentyl, hexyl, isohexyl, etc.); amino; aforementioned "protected carboxy"; and the like.

The acyl moiety as stated above may have one to ten, same or different, suitable substituent(s) such as lower alkyl (e.g., methyl, ethyl, propyl, etc.);
lower alkoxy (e.g., methoxy, ethoxy, propoxy, etc.);
lower alkylthio (e.g., methylthio, ethylthio, etc.);
mono-(or di-)lower alkylamino which may have one or more suitable substituent(s) (e.g., methylamino, ethylamino, propylamino, dimethylamino, diethylamino, dipropylamino, N-methoxy-N-methylamino, N-ethoxy-N-ethylamino, N-methoxymethyl-N-methylamino, N-methoxyethyl-N-methylamino, etc.); lower alkanoylamino (e.g., acetylamino, propionylamino, butyrylamino, pentanoylamino, hexanoylamino, etc.); cyclo(lower)alkylamino (e.g., cyclopropylamino, cyclobutylamino, cyclopentylamino, cyclohexylamino, etc.);
mono-(or di-)lower alkoxy(lower)alkylamino (e.g., methoxymethylamino, methoxyethylamino, methoxypropylamino, ethoxymethylamino, ethoxyethylamino, ethoxypropylamino, etc.); hydroxy(lower)alkylamino (e.g., hydroxymethylamino, hydroxyethylamino, hydroxypropylamino, hydroxypentylamino, hydroxyhexylamino, etc.); heterocyclic(lower)alkylamino, in which "heterocyclic moiety" is aforementioned "heterocyclic" moiety;

heterocyclicamino which may have one or more suitable substituent(s), in which "heterocyclic" moiety is aforementioned "heterocyclic" moiety;
lower alkanoyloxy (e.g., acetyloxy, propionyloxy, butyryloxy, pentanoyloxy, hexanoyloxy, etc.);
heterocyclic group, in which "heterocyclic group" is aforementioned "heterocyclic group";
di-lower alkoxy(lower)alkyl (e.g., dimethoxymethyl, dimethoxyethyl, dimethoxypropyl, diethoxymethyl, diethoxyethyl, diethoxypropyl, etc.);
arylamino which may have one or more suitable substituent(s) (e.g., phenylamino, dimethylaminophenylamino, trifluoromethylphenylamino, trifluoromethylnaphthylamino, trifluoromethylanthrylamino, etc.);
cyano(lower)alkylamino (e.g., cyanomethylamino, cyanoethylamino, cyanopropylamino, cyanobutylamino, cyanopentylamino, cyanohexylamino, etc.);
arylsulfonylamino (e.g., phenylsulfonylamino naphthylsulfonylamino, anthrylsulfonylamino, etc.);
protected carboxy(lower)alkylamino (e.g., methoxycarbonylmethylamino, methoxycarbonylethylamino, ethoxycarbonylmethylamino, ethoxycarbonylethylamino, etc.);
tri-halo(lower)alkylamino (e.g., 2,2,2-trifluoroethylamino, 1-(trifluoromethyl)ethylamino, 2-(trifluoromethyl)propylamino, etc.);
cyclo(lower)alkyl (e.g., cyclopentyl, cyclohexyl, etc.);
cyclo(lower)alkenyl (e.g., cyclohexenyl, cyclohexadienyl, etc.);
halogen (e.g., fluorine, chlorine, bromine, iodine, etc.);
amino, commonly protected amino as mentioned above; hydroxy; commonly protected hydroxy as mentioned below; cyano; nitro; carboxy; carboxy(lower)alkyl;
commonly protected carboxy as mentioned below; sulfo; sulfamoyl; imino; oxo; hydrazino; amino(lower)alkyl (e.g., aminomethyl, aminoethyl, etc.); carbamoyloxy;

hydroxy(lower)alkyl (e.g., hydroxymethyl, 1-(or 2-)-hydroxyethyl, 1-(or 2- or 3-)hydroxypropyl, etc.), or the like.

Suitable "hydroxy protective group" in the term commonly "protected hydroxy" may include acyl as mentioned above, phenyl(lower)alkyl which may have one or more suitable substituent(s) (e.g., benzyl, 4-methoxybenzyl, trityl, etc.), trisubstituted silyl [e.g., tri(lower)alkylsilyl (e.g., trimethylsilyl, t-butyldimethylsilyl, etc.), etc.], tetrahydropyranyl and the like.

Suitable commonly "protected carboxy" may include esterified carboxy and the like. And suitable example of said ester may be the ones such as lower alkyl ester (e.g., methyl ester, ethyl ester, propyl ester, isopropyl ester, butyl ester, isobutyl ester, t-butyl ester, pentyl ester, t-pentyl ester, hexyl ester, etc.);
lower alkenyl ester (e.g., vinyl ester, allyl ester, etc.);
lower alkynyl ester (e.g., ethynyl ester, propynyl ester, etc.);
lower alkoxy(lower)alkyl ester (e.g., methoxymethyl ester, ethoxymethyl ester, isopropoxy ester, 1-methoxyethyl ester, 1-ethoxyethyl ester, etc.);
lower alkylthio(lower)alkyl ester (e.g., methylthiomethyl ester, ethylthiomethyl ester, ethylthioethyl ester, isopropoxythiomethyl ester, etc.);
mono-(or di- or tri-)halo(lower)alkyl ester (e.g., 2-iodoethyl ester, 2,2,2-trichloroethyl ester, etc.);
lower alkanoyloxy(lower)alkyl ester (e.g., acetoxymethyl ester, propionyloxymethyl ester, butyryloxymethyl ester, valeryloxymethyl ester, pivaloyloxymethyl ester, hexanoyloxymethyl ester, 1-acetoxyethyl ester, 2-acetoxyethyl ester, 2-propionyloxyethyl ester, etc.);
lower alkoxycarbonyloxy(lower)alkyl ester (e.g., methoxycarbonyloxymethyl ester, ethoxycarbonyloxymethyl ester, propoxycarbonyloxymethyl ester,

1-(or 2-)[methoxycarbonyloxy]ethyl ester,
1-(or 2-)[ethoxycarbonyloxy]ethyl ester,
1-(or 2-)[propoxycarbonyloxy]ethyl ester,
1-(or 2-)[isopropoxycarbonyloxy]ethyl ester, etc.);
lower alkanesulfonyl(lower)alkyl ester (e.g., mesylmethyl ester, 2-mesyethyl ester, etc.);
lower alkoxycarbonyloxy(lower)alkyl ester (e.g., methoxycarbonyloxymethyl ester, ethoxycarbonyloxymethyl ester, propoxycarbonyloxymethyl ester,
t-butoxycarbonyloxymethyl ester,
1-(or 2-)methoxycarbonyloxyethyl ester,
1-(or 2-)ethoxycarbonyloxyethyl ester,
1-(or 2-)propoxycarbonyloxyethyl ester,
1-(or 2-)isopropoxycarbonyloxyethyl ester, etc.);
phthalidylidene(lower)alkyl ester, or
(5-lower alkyl-2-oxo-1,3-dioxol-4-yl)(lower)alkyl ester [e.g., (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl ester, (5-ethyl-2-oxo-1,3-dioxol-4-yl)methyl ester, (5-propyl-2-oxo-1,3-dioxol-4-yl)ethyl ester, etc.];
ar(lower)alkyl ester, for example, phenyl(lower)alkyl ester which may have one or more suitable substituent(s) (e.g., benzyl ester, 4-methoxybenzyl ester, 4-nitrobenzyl ester, phenethyl ester, trityl ester, benzhydryl ester, bis(methoxyphenyl)methyl ester, 3,4-dimethoxybenzyl ester, 4-hydroxy-3,5-di-t-butylbenzyl ester, etc.);
aryl ester which may have one or more suitable substituent(s) such as substituted or unsubstituted phenyl ester (e.g., phenyl ester, tolyl ester, t-butylphenyl ester, xylyl ester, mesityl ester, cumenyl ester, 4-chlorophenyl ester, 4-methoxyphenyl ester, etc.);
tri(lower)alkyl silyl ester; lower alkylthioester (e.g., methylthioester, ethylthioester, etc.) and the like.

The preferred examples of "an acyl group" may be carboxy protected carboxy, carbamoyl, lower alkanoyl, lower

alkylsulfonyl, aroyl, heterocyclic carbonyl which may have one or more suitable substituent(s), in which the more preferred one may be carboxy, (C_1-C_4)alkoxy carbonyl, carbamoyl, (C_1-C_4)alkanoyl, (C_1-C_4)alkylsulfonyl, benzoyl, carbonyl substituted with unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s), carbamoyl substituted with saturated 3 to 8-membered heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), carbonyl substituted with saturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) having (C_1-C_4)alkyl, and the most preferred one may be carboxy, methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl, carbamoyl, acetyl, methylsulfonyl, benzoyl, morpholinocarbonyl, N-methylpiperidylcarbonyl or pyridylcarbonyl.

Suitable "acyl" moiety in the term of "acylamino" can be referred to aforementioned "acyl" moiety.

The preferred examples of "acylamino" may be ureido, lower alkanoylamino, lower alkoxycarbonylamino, heterocyclic carbonylamino, lower alkanoylamino(lower)alkanoylamino (e.g. acetylaminoacetylamino, acetylaminopropionylamino, propionylaminoacetylamino, propionylaminopropionylamino, etc.), mono-(or di-)lower alkylamino(lower)alkanoylamino (e.g., methylaminoacetylamino, dimethylaminoacetylamino, ethylaminoacetylamino, diethylaminoacetylamino, etc.), lower alkanoyloxy(lower)alkanoylamino (e.g., acetyloxyacetylamino, acetyloxypropionylamino, propionyloxyacetylamino, propionyloxypropionylamino, etc.), heterocyclic(lower)alkanoylamino (e.g., heterocyclic-carbonylamino, heterocyclic-acetylamino, heterocyclic-propionylamino, etc.), lower alkoxy(lower)alkanoylamino (e.g., methoxyacetylamino, ethoxyacetylamino, methoxypropionylamino, ethoxypropionylamino, etc.), hydroxy(lower)alkanoylamino (e.g., hydroxyacetylamino,

hydroxypropionylamino, etc.), lower alkylsulfonylamino (e.g., methylsulfonylamino, ethylsulfonylamino, propylsulfonylamino, butylsulfonylamino, pentylsulfonylamino, hexylsulfonylamino, etc.), or mono-(or di-)lower alkoxy(lower)alkylamino(lower)-alkanoylamino (e.g., methoxymethylaminoacetylamino, bis(methoxymethyl)aminoacetylamino, methoxyethylaminoacetylamino, bis(methoxyethyl)aminoacetylamino, etc.), in which the more preferred one may be ureido, (C_1-C_4)alkanoylamino, (C_1-C_4)alkoxycarbonylamino, carbonylamino substituted with saturated 3 to 8-membered heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), (C_1-C_4)-alkanoylamino(C_1-C_4)alkanoylamino, di(C_1-C_4)alkylamino-(C_1-C_4)alkanoylamino, (C_1-C_4)alkanoyloxyC_1-C_4)alkanoylamino, (C_1-C_4)alkanoylamino substituted with saturated 3 to 8-membered heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), (C_1-C_4)alkoxy(C_1-C_4)-alkanoylamino, hydroxy(C_1-C_4)alkanoylamino, (C_1-C_4)-alkylsulfonylamino or bis[(C_1-C_4)alkoxy(C_1-C_4)alkyl]amino (C_1-C_4)alkanoylamino and the most preferred one may be ureido, acetylamino, t-butoxycarbonylamino, morpholinocarbonylamino, acetylaminoacetylamino, dimethylaminoacetylamino, acetyloxyacetylamino, morpholinoacetylamino, methoxyacetylamino, hydroxyacetylamino, methylsulfonylamino or dimethoxyethylaminoacetylamino.

Suitable "hydroxy(lower)alkyl" moiety in the term of "hydroxy(lower)alkyl which may have one or more suitable substituent(s)" may be hydroxymethyl, 1-(or 2-)hydroxyethyl, 1-hydroxy-1-methylethyl, 2-hydroxypropyl, 1-hydroxy-1-ethylethyl, 1-hydroxy-1-ethylpropyl, 1-hydroxybutyl, 1-(or 2- or 3-)hydroxy-1-(or 2- or 3-)methylpropyl, 1-(or 2- or 3- or 4-)hydroxy-1-(or 2- or 3- or 4-)methylbutyl, 1-(or 2- or 3- or 4- or 5-)hydroxy-1-(or 2- or 3- or 4- or 5-)methylpentyl,

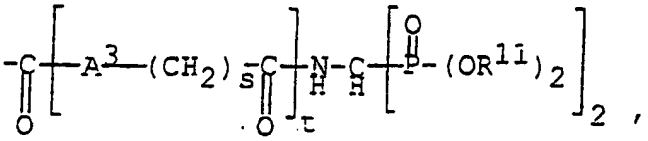
1-(or 2- or 3- or 4- or 5- or 6-)hydroxy-1-(or 2- or 3- or 4- or 5- or 6-)methylhexyl, or the like.

The preferred examples of "hydroxy(lower)alkyl" may be hydroxy(C_1-C_5)alkyl, and the most preferred one may be hydroxymethyl, 1-hydroxyethyl, 1-hydroxy-1-methylethyl, 1-hydroxy-1-ethylpropyl, 1-hydroxybutyl, 2-hydroxyethyl, 3-hydroxy-3-methylbutyl, 1-hydroxybutyl, 2-hydroxypropyl or 2-hydroxy-2-methylpropyl.

The preferred examples of "suitable substituent(s)" in the term of "hydroxy(lower)alkyl which may have one or more suitable substituent(s)" may be mono-(or di- or tri-)-halo(lower)alkyl, protected carboxy, hydroxy, aryl, cyclo(lower)alkyl or heterocyclic group, in which the preferred one may be tri-halo(C_1-C_4)alkyl, (C_1-C_4)-alkoxycarbonyl, hydroxy, phenyl, cyclo(C_3-C_6)alkyl, or unsaturated heteromonocyclic group consisting of 1 to 4 nitrogen atom(s), and the most preferred one may be trifluoromethyl, ethoxycarbonyl, hydroxy, phenyl, cyclohexyl or pyridyl.

Suitable "acyl" moiety in the term of "acyl(lower)alkyl" can be referred to aforementioned "acyl" moiety.

The preferred examples of "acyl(lower)alkyl" may be carboxy(lower)alkyl, protected carboy(lower)alkyl, carbamoyl(lower)alkyl, lower alkanoyl(lower)alkyl, aroyl(lower)alkyl, carbonyl(lower)alkyl substituted with heterocyclic group which may have one or more suitable substituent(s), sulfonyl(lower)alkyl substituted with heterocyclic group which may have one or more suitable substituent(s), sulfinyl(lower)alkyl substituted with heterocyclic group which may have one or more suitable substituent(s), lower alkyl having

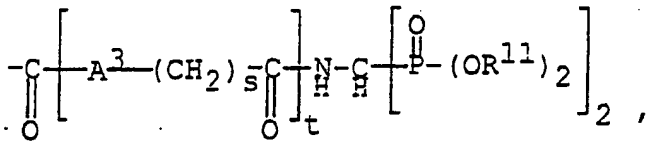


(wherein A^3 is lower alkylene, amino lower alkylene or aminophenylene,
R^{11} is lower alkyl or hydrogen, and
s and t are each integer of 1 to 6),

(mono- or di-)lower alkylaminocarbonyl(lower)alkyl which may have one or more suitable substituent(s) (e.g., methylaminocarbonylmethyl, dimethylaminocarbonylmethyl, methylaminocarbonylethyl, 2-dimethylaminocarbonylethyl, N-methoxy-N-methylaminocarbonylmethyl, N-methoxyethyl-N-methylaminocarbonylmethyl, trifluoromethylaminocarbonylmethyl, trifluoroethylaminocarbonylmethyl, cyanomethylaminocarbonylmethyl, cyanoethylaminocarbonylmethyl, cyanomethylaminocarbonylethyl, etc.), cyclo(lower)alkylaminocarbonyl(lower)alkyl (e.g. cyclopropylaminocarbonylmethyl, cyclobutylaminocarbonylmethyl, cyclopentylaminocarbonylmethyl, cyclohexylaminocarbonylmethyl, etc.), lower alkoxy(lower)alkylaminocarbonyl(lower)alkyl (e.g., methoxymethylaminocarbonylmethyl, methoxyethylaminocarbonylmethyl, methoxypropylaminocarbonylmethyl, bis(methoxymethylamino)carbonylmethyl, bis(methoxyethylamino)carbonylmethyl, etc.), di-(lower)alkoxyphosphoryl(lower)alkyl (e.g., dimethoxyphosphorylmethyl, diethoxyphosphorylmethyl,

dipropoxyphosphorylethyl, dibutoxyphosphorylethyl, dipentyl-oxyphosphorylethyl, dihexyloxyphosphorylpropyl, etc.), mono-(or di-)hydroxy(lower)alkylaminocarbonyl(lower)alkyl (e.g., hydroxymethylaminocarbonylmethyl, hydroxyethylaminocarbonylmethyl, dihydroxymethylaminocarbonylmethyl, dihydroxyethylaminocarbonylmethyl, etc.), aminocarbonyl(lower)alkyl substituted with heterocyclic group which may have one or more suitable substituent(s) (e.g. thiazolylaminocarbonylmethyl, piperidinoaminocarbonylmethyl, morpholinoaminomethyl, methyloxadiazolylaminocarbonylmethyl, trifluoromethylthiadiazolylaminocarbonylmethyl, pyridylamino-carbonylmethyl, aminopyridylaminocarbonylmethyl, etc.), heterocyclic(lower)alkylaminocarbonyl(lower)alkyl (e.g., pyridylmethylaminocarbonylmethyl, tetrahydrofuranylmethylaminocarbonylmethyl, furanylmethylaminocarbonylmethyl, morpholinoethylaminocarbonylmethyl, thienylmethylaminocarbonylmethyl, imidazolylethylaminocarbonylmethyl, etc.), hydrazinocarbonyl(lower)alkyl (e.g., hydrazinocarbonylmethyl, hydrazinocarbonylethyl, hydrazinocarbonylpropyl, etc.), aminocarbonyl(lower)alkyl substituted with aryl which may have one or more suitable substituent(s) (e.g., dimethylaminophenylaminocarbonylmethyl, trifluoromethylphenylaminocarbonylmethyl, anilinophenylaminocarbonylmethyl, aminophenylaminocarbonylmethyl, etc.), cyano(lower)alkylaminocarbonyl(lower)alkyl (e.g., cyanomethylaminocarbonylmethyl, cyanoethylaminocarbonylmethyl, cyanomethylaminocarbonylethyl, cyanoethylaminocarbonylethyl, etc.), arylsulfonylaminocarbonyl(lower)alkyl (e.g., phenylsulfonylaminocarbonylmethyl, phenylsulfonylaminocarbonylethyl,

phenylsulfonylaminocarbonylpropyl, etc.),
protected carboxy(lower)alkylaminocarbonyl(lower)alkyl (e.g. methoxycarbonylmethylaminocarbonylmethyl, ethoxycarbonylmethylaminocarbonylmethyl, 1-(or 2-)methoxycarbonylethylaminocarbonylmethyl, 1-(or 2-)ethoxycarbonylethylaminocarbonylethyl, etc.), in which the preferred one may be (C_1-C_4)alkoxycarbonyl-(C_1-C_4)alkyl, (C_1-C_4)alkanoyl(C_1-C_4)alkyl, carbamoyl-(C_1-C_4)alkyl, carboxy(C_1-C_4)alkyl, lower alkyl having



(wherein A^3 is (C_1-C_6)alkylene, amino(C_1-C_6)alkylene or aminophenylene,
R^{11} is (C_1-C_6)alkyl or hydrogen, and
s and t are each integer of 1 to 6),

carbonyl(C_1-C_4)alkyl substituted with heterocyclic group which may have 1 to 3 suitable substituent(s),
sulfonyl(C_1-C_4)alkyl substituted with heterocyclic group which may have 1 to 3 suitable substituent(s),
sulfinyl(C_1-C_4)alkyl substituted with heterocyclic group which may have 1 to 3 suitable substituent(s),
mono-(or di-)(C_1-C_4)alkylaminocarbonyl(C_1-C_4)alkyl which may have 1 to 3 suitable substituent(s),
cyclo(C_3-C_6)alkylaminocarbonyl(C_1-C_4)alkyl,
(C_1-C_4)alkoxy(C_1-C_4)alkylaminocarbonyl(C_1-C_4)alkyl,
di-(C_1-C_4)alkoxyphosphoryl(C_1-C_4)alkyl,
mono-(or di-)hydroxy(C_1-C_4)alkylaminocarbonyl(C_1-C_4)alkyl,
aminocarbonyl(C_1-C_4)alkyl substituted with heterocyclic group

which may have 1 to 3 suitable substituent(s), heterocyclic(C_1-C_4)alkylaminocarbonyl(C_1-C_4)alkyl, hydrazinocarbonyl(C_1-C_4)alkyl, aminocarbonyl(C_1-C_4)alkyl substituted with phenyl which may have 1 to 3 suitable substituent(s), cyano(C_1-C_4)alkylaminocarbonyl(C_1-C_4)alkyl, phenylsulfonylaminocarbonyl(C_1-C_4)alkyl, (C_1-C_4)alkoxycarbonyl(C_1-C_4)alkylaminocarbonyl(C_1-C_4)alkyl, and the most preferred one may be carboxymethyl, carboxyethyl, methoxycarbonylmethyl, methoxycarbonylethyl, ethoxycarbonylmethyl, ethoxycarbonylethyl, benzoylmethyl, carbamoylmethyl, acetylmethyl, t-butoxycarbonylmethyl, morpholinocarbonylmethyl, pyridylcarbonylmethyl, chlorothienylcarbonylmethyl, pyrrolinylcarbonylmethyl, acetylpiperazinylcarbonylmethyl, phenylpiperazinylcarbonylmethyl, methylpiperazinylcarbonylmethyl, hydroxypiperidinocarbonylmethyl, 4-pyridylpiperazinylcarbonylmethyl, imidazolylsulfonylmethyl, methylimidazolylsulfonylmethyl, imidazolylsulfinylmethyl, dimethylaminocarbonylmethyl, dimethylaminocarbonylethyl, trifluoromethylmethylaminocarbonylmethyl, cyanomethylaminocarbonylmethyl, cyclopentylaminocarbonylmethyl, methoxyethylaminocarbonylmethyl, dimethoxyethylaminocarbonylmethyl, N-methoxy-N-methylaminocarbonylmethyl, N-methoxyethyl-N-methylaminocarbonylmethyl, dimethoxyphosphorylmethyl, diethoxyphosphorylmethyl, hydroxyethylaminocarbonylmethyl, dihydroxyethylaminocarbonylmethyl, trifluoromethylthiadiazolylaminocarbonylmethyl, thiazolylaminocarbonylmethyl, piperidinoaminocarbonylmethyl, morpholinoaminocarbonylmethyl, pyridyl-N-methylaminocarbonylmethyl, methyloxadiazolylaminocarbonylmethyl,

pyridylaminocarbonylmethyl, aminopyridylaminocarbonylmethyl, pyridylmethylaminocarbonylmethyl, tetrahydrofuranylmethylaminocarbonylmethyl, trifluorothiadiazolylaminocarbonylmethyl, furanylmethylaminocarbonylmethyl, morpholinoethylaminocarbonylmethyl, thienylmethylaminocarbonylmethyl, imidazolylethylaminocarbonylmethyl, anilinophenylaminocarbonylmethyl, aminophenylaminocarbonylmethyl, hydrazinocarbonylmethyl, dimethylaminophenylaminocarbonylmethyl, trifluoromethylphenylaminocarbonylmethyl, phenylsulfonylaminocarbonylmethyl, 1-methoxycarbonylethylaminocarbonylmethyl or ethoxycarbonylmethylaminocarbonylmethyl.

The preferred examples of "mono-(or di- or tri-)-halo(lower)alkyl" may be fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, bromomethyl, dibromomethyl, tribromomethyl, 1-(or 2-)fluoroethyl, 1-(or 2-)bromoethyl, 1-(or 2-)chloroethyl, 1,1-difluoroethyl, 2,2-difluoroethyl, or the like, in which the preferred one may be mono-(or di- or tri-)halo(C_1-C_4)alkyl, and the most preferred one may be difluoromethyl or trifluoromethyl.

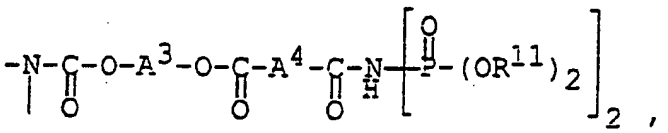
The preferred examples of "lower alkylthio" may be methylthio, ethylthio, propylthio, butylthio, pentylthio, hexylthio, or the like, in which the preferred one may be (C_1-C_4)alkylthio, and the most preferred one may be methylthio.

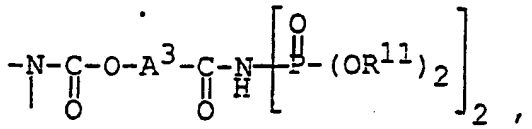
The preferred examples of "cyclo(lower)alkyl(lower)alkyl" may be cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl,

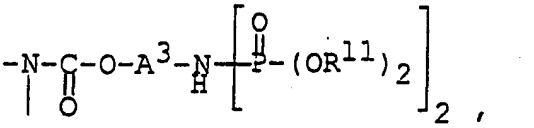
cyclopropylethyl, cyclobutylethyl, cyclopentylethyl, cyclohexylethyl, or the like, in which the preferred one may be cyclo(C_3-C_6)alkyl(C_1-C_4)alkyl, and the most preferred one may be cyclohexylmethyl.

Suitable "acylamino" moiety in the term of "acylamino-(lower)alkyl" can be referred to aforementioned "acylamino".

The preferred examples of "acylamino(lower)alkyl" may be lower alkoxycarbonylamino(lower)alkyl, lower alkanoylamino(lower)alkyl, heterocyclic-carbonylamino-(lower)alkyl,







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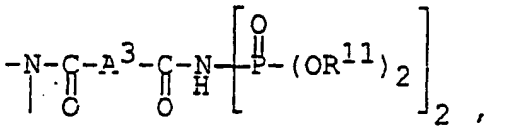
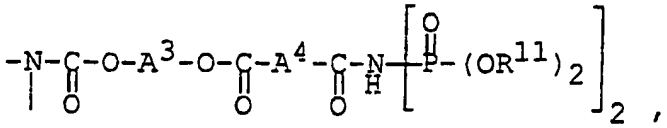
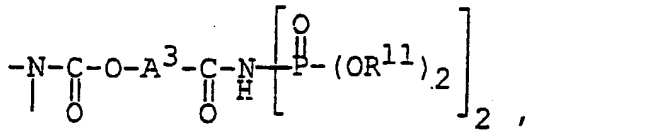
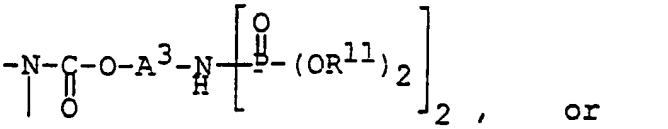


(wherein A^3 and A^4 are each lower alkylene, amino(lower)alkylene or aminophenylene, and R^{11} is lower alkyl or hydrogen),

in which the preferred one may be (C_1-C_4)alkoxycarbonylamino-(C_1-C_4)alkyl, (C_1-C_4)alkanoylamino(C_1-C_4)alkyl, carbonylamino(C_1-C_4)alkyl substituted with saturated 3 to 8-membered heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s),







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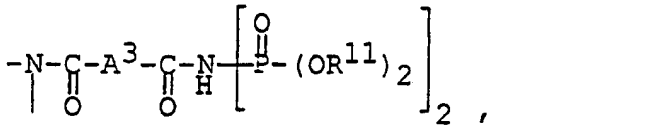


(wherein A^3 and A^4 are each (C_1-C_6)alkylene, amino(C_1-C_6)-alkylene or aminophenylene, and R^{11} is (C_1-C_6)alkyl or hydrogen),

and the most preferred one may be t-butoxycarbonyl aminomethyl, acetylaminomethyl or morpholinocarbonylaminomethyl.

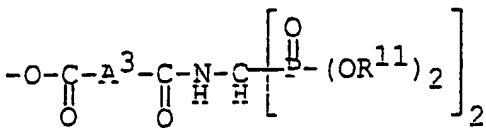
Suitable "acyl" moiety in the terms of "acyl(lower)alkenyl" can be referred to aforementioned "acyl" moiety.

Suitable "(lower)alkenyl" moiety in the term of "acyl(lower)alkenyl" can be referred to aforementioned "lower alkenyl".

The preferred examples of "acyl(lower)alkenyl" may be protected carboxy(lower)alkenyl, in which the preferred one may be (C_1-C_4)alkoxycarbonyl(C_1-C_4)alkenyl, and the most preferred one may be ethoxycarbonylvinyl.

Suitable "acyl" moiety in the term of "acyloxy(lower)alkyl" can be referred to aforementioned "acyl" moiety.

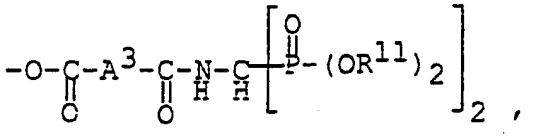
The preferred examples of "acyloxy(lower)alkyl" may be lower alkanoyloxy(lower)alkyl, cyclo(lower)alkylcarbonyloxy(lower)alkyl, carboxy(lower)alkanoyloxy(lower)alkyl, protected carboxyoxy(lower)alkyl, protected carboxy(lower)alkanoyloxy(lower)alkyl, lower alkylaminocarbonyloxy(lower)alkyl, aroyloxy(lower)alkyl, or lower alkyl substituted with



(wherein A^3 is lower alkylene, amino(lower)alkylene or aminophenylene, and

R^{11} is lower alkyl or hydrogen),

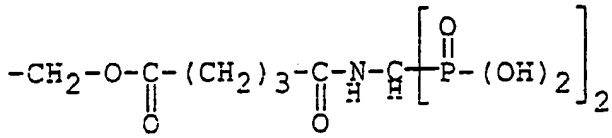
in which the preferred one may be (C_1-C_4)alkanoyloxy-(C_1-C_4)alkyl, cyclo(C_3-C_6)alkylcarbamoyloxy-(C_1-C_4)alkyl, carboxy(C_2-C_4)alkanoyloxy-(C_1-C_4)alkyl, succinimidoxycarbonyl-(C_2-C_4)alkanoyloxy(C_1-C_4)alkyl, (C_1-C_4)-alkylaminocarbonyloxy(C_1-C_4)alkyl, (C_1-C_4)alkoxycarbonyloxy(C_1-C_4)alkyl, benzoyloxy(C_1-C_4)alkyl, or lower alkyl substituted with



(wherein A^3 is (C_1-C_6)alkylene, amino(C_1-C_6)alkylene or aminophenylene, and

R^{11} is (C_1-C_6)alkyl or hydrogen),

and the most preferred one may be acetyloxymethyl, 1-acetyloxyethyl, cyclohexylcarbonyloxymethyl, methoxycarbonyloxymethyl, carboxybutanoyloxymethyl, succinimidyloxycarbonylbutanoyloxymethyl, ethylaminocarbonyloxymethyl,



ethoxcarbonyloxymethyl or benzoyloxymethyl.

Suitable "acyl" moiety in the term of "acyl(lower)alkylthio(lower)alkyl" can be referred to aforementioned "acyl" moiety.

The preferred examples of "acyl(lower)alkylthio(lower)alkyl" may be protected carboxy(lower)alkylthio(lower)alkyl, in which the preferred one may be (C_1-C_4)alkoxycarbonyl(C_1-C_4)alkylthio(C_1-C_4)alkyl, and the most preferred one may be ethoxycarbonylmethylthiomethyl.

The preferred examples of "amino(lower)alkyl" may be amino(C_1-C_4)alkyl, in which the most preferred one may be aminomethyl.

The preferred examples of "mono-(or di-)lower alkylamino" may be methylamino, dimethylamino, ethylamino, diethylamino, propylamino, dipropylamino, butylamino, dibutylamino, pentylamino, dipentylamino, hexylamino, dihexylamino, or the like, in which the preferred one may be mono-(or di-)(C_1-C_4)alkylamino, and the most preferred one may be methylamino, dimethylamino or diethylamino.

The preferred examples of "lower alkylthio(lower)alkyl" may be methylthiomethyl, methylthioethyl, methylthiopropyl, methylthiobutyl, ethylthiomethyl, ethylthioethyl, ethylthiopropyl, propylthiomethyl, propylthioethyl, propylthiopropyl, or the like, in which the preferred one may be (C_1-C_4)alkylthio(C_1-C_4)alkyl, and the most preferred one may be methylthiomethyl.

The preferred examples of "hydroxyimino(lower)alkyl which may have one or more suitable substituent(s)" may be hydroxyiminomethyl, 1-hydroxyiminoethyl, hydroxyimino-1-methylethyl, hydroxyimino-1-methylpropyl, hydroxyimino-1-methylpropyl, hydroxyimino-1-amino-methyl, 2-hydroxyimino-2-amino-ethyl, hydroxyimino-1-aminopropyl, or the like, in which the preferred one may be hydroxyimino(C_1-C_4)alkyl which may have amino, and the most preferred one may be

1-hydroxyiminoethyl or 2-hydroxyimino-2-aminoethyl.

The preferred examples of "hydroxy(lower)alkylthio(lower)alkyl" may be hydroxymethylthiomethyl, 2-hydroxymethylthioethyl, 2-hydroxymethylthiopropyl, 4-hydroxymethylthiobutyl, 5-hydroxymethylthiopentyl, hydroxymethylthiohexyl, (2-hydroxyethyl)thiomethyl, 2-(1-hydroxyethyl)thioethyl, (1- or 2-hydroxyethyl)thiopropyl, (1- or 2-hydroxyethyl)-thiobutyl, (1- or 2-hydroxyethyl)thiopentyl, (1- or 2-hydroxyethyl)thiohexyl, or the like, in which the preferred one may be hydroxy(C_1-C_4)alkylthio(C_1-C_4)alkyl, and the most preferred one may be (2-hydroxyethyl)thiomethyl.

The preferred examples of "cyano(lower)alkyl" may be cyanomethyl, 1-(or 2-)cyanoethyl, 1-(or 2- or 3-)cyanopropyl, 1-(or 2- or 3- or 4-)cyanobutyl, 1-(or 2- or 3- or 4- or 5-)-yanopentyl, 1-(or 2- or 3- or 4- or 5- or 6-)cyanohexyl, or the like, in which the preferred one may be cyano(C_1-C_4)-alkyl, and the most preferred one may be cyanomethyl or 2-cyanoethyl.

Suitable "mono-(or di-)lower alkoxy(lower)alkyl" may be methoxymethyl, methoxyethyl, dimethoxymethyl, dimethoxyethyl, ethoxymethyl, ethoxyethyl, diethoxymethyl, diethoxyethyl, propoxymethyl, propoxyethyl, propoxypropyl, dipropoxymethyl, dipropoxyethyl, dipropoxypropyl, or the like, in which the preferred one may be mono-(or di-)(C_1-C_4)alkoxy(C_1-C_4)alkyl, and the most preferred one may be methoxymethyl, 2-methoxyethyl or 3-diethoxypropyl.

The preferred examples of "mono-(or di-)lower alkoxy(lower)alkyl which may have one or more suitable substituent(s)" may be (C_1-C_4)alkoxy(C_1-C_4)alkyl or tri-halo(C_1-C_4)alkyl(C_1-C_4)alkoxy(C_1-C_4)alkyl, and the most preferred one may be methoxymethyl, 2-methoxyethyl,

3-diethoxypropyl or trifluoromethylmethoxymethyl.

Suitable "lower alkyl substituted with aryl" may be benzyl, phenethyl, 2-phenylpropyl, naphthylmethyl, naphthylethyl, anthrylmethyl, 1-anthrylethyl, or the like, in which the more preferred one may be phenyl(C_1-C_4)alkyl, naphthyl(C_1-C_4)alkyl or anthryl(C_1-C_4)alkyl, and the most preferred one may be benzyl.

The preferred examples of "lower alkyl substituted with aryl which may have one or more suitable substituent(s)" may be the one which may have 1 to 3 nitro or cyano, such as phenyl(C_1-C_4)alkyl, nitrophenyl(C_1-C_4)alkyl or cyanophenyl(C_1-C_4)alkyl, in which the most preferred one may be benzyl, 4-nitrobenzyl or 3-cyanobenzyl.

The preferred examples of "mono-(or di-)lower alkylaminc(lower)alkyl" may be mono-(or di-)(C_1-C_4)-lkylamino(C_1-C_4)alkyl, in which the more preferred one may be dimethylaminomethyl.

The preferred example of "tri(lower)alkylammonio(lower)-alkyl" may be trimethylammoniomethyl, triethylammonioethyl, tripropylammoniopropyl, tributylammoniobutyl, tripentylammoniopentyl, trihexylammoniohexyl, or the like, in which the preferred one may be tri(C_1-C_4)alkylammonio(C_1-C_4)-alkyl, and the most preferred one may be trimethylammoniomethyl.

Suitable "heterocyclic group" moiety in the term of "lower alkyl substituted with heterocyclic group which may have one or more suitable substituent(s)" can be referred to aforementioned "heterocyclic group".

The preferred examples of "lower alkyl substituted with heteocyclic group which may have one or more suitable substituent(s)" may be imidazolyl(lower)alkyl,

pyridyl(lower)alkyl, morpholino(lower)alkyl, pyrrolidinyl(lower)alkyl, tetrazolyl(lower)alkyl, piperidino(lower)alkyl, benzimidazolyl(lower)alkyl, triazolyl(lower)alkyl, oxiranyl(lower)alkyl, lower alkyl substituted with methylenedicxyphenyl having halogen, lower alkyl substituted with piperazine having (lower)alkyl, lower alkyl substituted with oxadiazole having (lower)alkyl, lower alkyl substituted with imidazole having aryl, lower alkyl substituted with imidazole having lower alkyl, lower alkyl substituted with piperidine having protected carboxy, lower alkyl substituted with pyrazole having hydroxy and lower alkyl, lower alkyl substituted with oxadiazole having lower alkyl, lower alkyl substituted with imidazopyridine, lower alkyl substituted with piperidine having hydroxy, lower alkyl substituted with piperazine having lower alkanoyl or lower alkyl substituted with piperazine having protected carboxy, in which the more preferred one may be imidazolyl(C_1-C_4)-alkyl, pyridyl(C_1-C_4)alkyl, morpholino(C_1-C_4)alkyl, pyrrolidinyl(C_1-C_4)alkyl, tetrazolyl(C_1-C_4)alkyl, oxiranyl(C_1-C_4)alkyl, piperidino(C_1-C_4)alkyl, benzimidazolyl(C_1-C_4)alkyl, triazolyl(C_1-C_4)alkyl, (C_1-C_4)alkyl substituted with methylenedioxyphenyl having halogen, (C_1-C_4)alkyl substituted with piperazine having (C_1-C_4)alkyl, (C_1-C_4)alkyl substituted with oxadiazole having (C_1-C_6)alkyl, (C_1-C_4)alkyl substituted with imidazole having phenyl, (C_1-C_4)alkyl substituted with imidazole having (C_1-C_4)alkyl, (C_1-C_4)alkyl substituted with piperidine having (C_1-C_4)alkoxycarbonyl, (C_1-C_4)alkyl substituted with pyrazole having hydroxy and (C_1-C_4)alkyl, (C_1-C_4)alkyl substituted with oxadiazole having (C_1-C_4)alkyl, (C_1-C_4)alkyl substituted with imidazopyridine, (C_1-C_4)alkyl substituted with piperidine having hydroxy, (C_1-C_4)alkyl substituted with piperazine having (C_1-C_4)alkanoyl or (C_1-C_4)alkyl substituted with piperazine having (C_1-C_4)alkoxycarbonyl, and the most preferred one may be imidazolylmethyl, pyridylmethyl,

3-pyridylpropyl, morpholinomethyl, 2-morpholinoethyl, 2-pyrrolidinylethyl, tetrazolylmethyl, oxiranylmethyl, chloromethylenedioxyphenylmethyl, N-methylpiperazinylpropyl, 5-methyloxadiazolylmethyl, 4-phenylimidazolylmethyl, 2-methylimidazolylmethyl, 4-ethoxycarbonylpiperidinomethyl, pyrrolidinylmethyl, piperidinomethyl, benzimidazolylmethyl, triazolylmethyl, 3-methyl-5-hydroxypyrazolylmethyl, 5-methyloxadiazolylmethyl, imidazopyridylmethyl, hydroxypiperidylmethyl, acetylpiperazinylmethyl, ethoxycarbonylpiperazinylmethyl or imidazolylethyl.

The preferred examples of "hydrazino(lower)alkyl which may have one or more suitable substituent(s)" may be hydrazino(lower)alkyl having lower alkoxycarbonyl, in which the more preferred one may be hydrazino(C_1-C_4)alkyl having (C_1-C_4)alkoxycarbonyl, and the most preferred one may be tert-butoxycarbonylhydrazinomethyl.

The preferred examples of "[mono or di(lower)alkoxy-(lower)alkyl]amino(lower)alkyl" may be [mono or di(C_1-C_4)-alkoxy(C_1-C_4)alkyl]amino(C_1-C_4)alkyl, in which the more preferred one may be [di(C_1-C_4)alkoxy(C_1-C_4)alkyl]amino-(C_1-C_4)alkyl, and the most preferred one may be N,N-dimethoxyethylaminomethyl.

The preferred examples of "(lower)alkylamino(lower)alkyl which may have one or more suitable substituent(s)" may be (lower)alkylamino(lower)alkyl having heterocyclic group, (lower)alkylamino(lower)alkyl having cyclo(lower)alkyl, (lower)alkylamino(lower)alkyl having lower alkoxy(lower)-alkyl, (lower)alkylamino(lower)alkyl having heterocyclic(lower)alkyl, (lower)alkylamino(lower)alkyl having lower alkoxycarbonyl(lower)alkyl, (lower)alkylamino(lower)alkyl having carboxy(lower)alkyl, (lower)alkylamino(lower)alkyl having carbamoyl(lower)alkyl,

(lower)alkylamino(lower)alkyl having cyano(lower)alkyl, (lower)alkylamino(lower)alkyl having hydroxy(lower)alkyl, (lower)alkylamino(lower)alkyl having halo(lower)alkyl, (lower)alkylamino(lower)alkyl having heterocyclicthio-(lower)alkyl or (lower)alkylamino(lower)alkyl having [di-(lower)alkylamino](lower)alkyl, in which the more preferred one may be (C_1-C_4)alkylamino(C_1-C_4)alkyl having pyridyl, (C_1-C_4)alkylamino(C_1-C_4)alkyl having cyclo(C_3-C_6)alkyl, (C_1-C_4)alkylamino(C_1-C_4)alkyl having (C_1-C_4)alkoxy(C_1-C_4)-alkyl, (C_1-C_4)alkylamino(C_1-C_4)alkyl having pyridyl(C_1-C_4)-alkyl, (C_1-C_4)alkylamino(C_1-C_4)alkyl having (C_1-C_4)-alkoxycarbonyl(C_1-C_4)alkyl, (C_1-C_4)alkylamino(C_1-C_4)alkyl having carboxy(C_1-C_4)alkyl, (C_1-C_4)alkylamino(C_1-C_4)alkyl having carbamoyl(C_1-C_4)alkyl, (C_1-C_4)alkylamino(C_1-C_4)alkyl having cyano(C_1-C_4)alkyl, (C_1-C_4)alkylamino(C_1-C_4)alkyl having hydroxy(C_1-C_4)alkyl, (C_1-C_4)alkylamino(C_1-C_4)alkyl having halo(C_1-C_4)alkyl, (C_1-C_4)alkylamino(C_1-C_4)alkyl having imidazolylthio(C_1-C_4)alkyl or (C_1-C_4)alkylamino(C_1-C_4)alkyl having di(C_1-C_4)alkylamino(C_1-C_4)alkyl, and the most preferred one may be N-methyl-N-pyridylaminomethyl, N-methyl-N-cyclohexylaminomethyl, N-methyl-N-methoxyethylaminomethyl, N-methyl-N-pyridylmethylaminomethyl, N-methyl-N-pyridylethylaminomethyl, N-methyl-N-ethoxycarbonylmethylaminomethyl, N-methyl-N-carboxymethylaminomethyl, N-methyl-N-carbamoylmethylaminomethyl, N-methyl-N-cyanomethylaminomethyl, N-methyl-N-hydroxyethylaminomethyl, N-methyl-N-bromoethylaminomethyl, N-methyl-N-imidazolylthioethylaminomethyl or N-methyl-N-(N',N'-dimethyl)ethylaminomethyl.

Suitable "heterocyclic group" moiety in the term of "heterocyclic group which may have one or more suitable substituent(s)" can be referred to aforementioned

"heterocyclic group".

The preferred examples of "heterocyclic group which may have one or more suitable substituent(s)", may be furyl, pyridyl which may have 1 to 3 substituent(s) selected from the group consisting of halogen, lower alkoxycarbonyl, and lower alkyl, thiazolyl which may have 1 to 3 lower alkanoylamino, benzothienyl which may have 1 to 3 halogen, indolyl which may have 1 to 3 substituent(s) selected from the group consisting of halogen and lower alkyl, oxazolyl which may have 1 to 3 lower alkyl, pyranyl which may have 1 to 3 substituent(s) selected from the group consisting of lower alkyl and oxo, pyrrolyl which may have 1 to 3 lower alkyl, phthalimido which may have nitro, phthalimidine which may have nitro, piperidyl which may have 1 to 3 lower alkyl, dihydropyridyl which may have lower alkoxycarbonyl.

Suitable "heterocyclic" moiety in the term of "heterocyclicthio(lower)alkyl which may have one or more suitable substituent(s)" can be referred to aforementioned to "heterocyclic group".

The preferred examples of "heterocyclicthio(lower)alkyl which may have one or more suitable substituent(s)" may be imidazolylthio(lower)alkyl, imidazolylthio(lower)alkyl having lower alkyl, pyridylthio(lower)alkyl benzimidazolylthio(lower)alkyl, or imidazopyridylthio(lower)alkyl, in which the preferred one may be imidazolylthio(C_1-C_4)alkyl, imidazolylthio(C_1-C_4)alkyl having (C_1-C_4)alkyl, benzimidazolyl(C_1-C_4)alkyl, pyridylthio(C_1-C_4)alkyl or imidazopyridylthio(C_1-C_4)alkyl, and the most preferred one may be imidazolylthiomethyl, 3-methylimidazolylthiomethyl, benzimidazolylthiomethyl imidazolylthioethyl, pyridylthiomethyl or imidazopyridylthiomethyl.

Suitable "heterocyclic" moiety in the term of

"heterocyclicthio" can be referred to aforementioned "heterocyclic group".

The preferred examples of "heterocyclicthio" may be pyridylthio or imidazolylthio.

Suitable "heterocyclic" moiety in the term of "heterocyclic oxy" can be referred to aforementioned "heterocyclic group".

The preferred examples of "heterocyclic oxy" may be pyridyloxy.

Suitable "heterocyclic" moiety in the term of "heterocyclic oxy(lower)alkyl" can be referred to aforementioned "heterocyclic group".

The preferred examples of "heterocyclic oxy(lower)alkyl" may be pyridyloxy(lower)alkyl, in which the more preferred one may be pyridyloxy(C_1-C_4)alkyl, and the most preferred one may be pyridyloxymethyl.

The preferred examples of "aryl which may have one or more suitable substituents" may be phenyl, naphthyl, anthryl, phenyl having amino, phenyl having di(lower)alkylamino, phenyl having heterocyclic(lower)alkylamino, phenyl having di(lower)alkylamino(lower)alkanoylamino, phenyl having lower alkylsulfonylamino, phenyl having higher alkanoylamino, in which the most preferred one may be phenyl, aminophenyl, dimethylaminophenyl, furylmethylaminophenyl, dimethylaminoacetylaminophenyl, methylsulfonylaminophenyl, lauroylaminophenyl.

Suitable "heterocyclic" moiety in the term of "heterocyclic aminoimino(lower)alkyl" can be referred to aforementioned "heterocyclic group".

The preferred examples of "heterocyclic aminoimino(lower)alkyl" may be aminoimino(lower)alkyl

substituted with unsaturated 3 to 8-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s), in which the more preferred one may be pyridylaminoimino(C_1-C_4)alkyl, and the most preferred one may be 2-pyridylaminoiminopropyl.

The preferred examples of "suitable substituent(s)" in the terms of "lower alkylene which may have one or more suitable substituent(s)" and "lower alkenylene which may have one or more suitable substituent(s)" may be lower alkyl, hydroxy, oxo, or the like, in which the preferred one may be (C_1-C_4)alkyl, hydroxy or oxo, and the most preferred one may be methyl, hydroxy or oxo.

The preferred examples of "suitable substituent(s)" in the terms of "aryl which may have one or more suitable substituent(s)" may be halogen, lower alkyl, nitro, lower alkoxy, an acyl group, cyclo(lower)alkyl, mono-(or di- or tri-)halo(lower)alkyl, acylamino, aryl, amino, mono-(or di-)-lower alkylamino, aryloxy, acyl(lower)alkyl, hydroxy, hydroxy(lower)alkyl which may have one or more suitable substituent(s), heterocyclic group which may have one or more suitable substituent(s), mono-(or di-)lower alkylamino(lower)alkyl or acyl(lower)alkyl.

The preferred examples of "mono-(or di-)lower alkylamino(lower)alkyl" may be mono-(or di-)(C_1-C_4)-alkylamino(C_1-C_4)alkyl, in which the preferred one may be di(C_1-C_4)alkylamino(C_1-C_4)alkyl, and the most preferred one may be dimethylaminomethyl.

Suitable "acyl" moiety in the term of "acyl(lower)alkoxy" can be referred to aforementioned "acyl" moiety.

The preferred examples of "acyl(lower)alkoxy" may be protected carboxy(lower)alkoxy, in which the more preferred

one may be (C_1-C_4)alkoxycarbonyl(C_1-C_4)alkoxy, and the most preferred one may be ethoxycarbonylmethoxy.

The preferred examples of "suitable substituent(s)" in the term of "naphthyl which may have one or more suitable substituent(s)" may be lower alkoxy, in which the more preferred one may be (C_1-C_4)alkoxy, and the most preferred one may be methoxy.

Suitable "acyl" moiety in the term of "acyl(lower)alkenyl" can be referred to aforementioned "acyl" moiety.

Suitable "(lower)alkenyl" moiety in the term of "acyl(lower)alkenyl" can be referred to aforementioned "lower alkenyl".

The preferred examples of "acyl(lower)alkenyl" may be protected carboxy(C_2-C_6)alkenyl, in which the more preferred one may be lower alkoxycarbonyl(C_2-C_4)alkenyl, and the most preferred one may be ethoxycarbonylvinyl.

The preferred examples of "aryloxy" may be phenoxy, naphthyloxy, anthryloxy, or the like, in which the most preferred one may be phenoxy.

The preferred examples of "aryl(lower)alkoxy" may be phenyl(C_1-C_6)alkoxy, naphthyl(C_1-C_6)alkoxy, anthryl(C_1-C_6)-alkoxy, or the like, in which the preferred one may be phenyl(C_1-C_4)alkoxy, and the most preferred one may be phenylmethoxy.

The preferred examples of "halo(lower)alkyl" may be chloromethyl, chloroethyl, bromomethyl, bromoethyl, fluoromethyl, fluoroethyl, iodopropyl, iodobutyl or the like, in which the more preferred one may be halo(C_1-C_4)alkyl, and the most preferred one may be chloromethyl or bromoethyl.

The preferred examples of "hydroxy(lower)alkylimino-(lower)alkyl" may be hydroxy(C_1-C_4)alkylimino(C_1-C_4)alkyl, in which the more preferred one may be hydroxyethyliminomethyl.

The preferred examples of "hydroxy(lower)alkylamino-(lower)alkyl" may be hydroxy(C_1-C_4)alkylamino(C_1-C_4)alkyl, in which the more preferred one may be hydroxyethylaminomethyl.

The preferred examples of "bis-[hydroxy(lower)alkyl]-amino(lower)alkyl" may be bis-[hydroxy(C_1-C_4)alkyl]amino-(C_1-C_4)alkyl, in which the more preferred one may be bis-[hydroxyethyl]aminomethyl.

The preferred examples of "mercapto(lower)alkyl" may be mercapto(C_1-C_4)alkyl, in which the more preferred one may be mercaptomethyl.

The preferred examples of "amidinothio(lower)alkyl" may be amidinothio(C_1-C_4)alkyl, in which the more preferred one may be amidinothiomethyl.

The processes for preparing the object compound (I) of the present invention are explained in detail in the following.

Process 1

The compound (Ia) or a salt thereof can be prepared by reacting the compound (II) or its reactive derivative at the amino group or a salt thereof with the compound (III) or its reactive derivative at the carboxy group or sulfo group or a salt thereof.

Suitable reactive derivative at the amino group of the compound (II) may include Schiff's base type imino or its tautomeric enamine type isomer formed by the reaction of the compound (II) with a carbonyl compound such as aldehyde,

ketone or the like; a silyl derivative formed by the reaction of the compound (II) with a silyl compound such as N,O-bis(trimethylsilyl)acetamide, N-trimethylsilylacetamide or the like; a derivative formed by the reaction of the compound (II) with phosphorus trichloride or phosgene, and the like.

Suitable reactive derivative of the compound (III) may include an acid halide, an acid anhydride, an activated ester, and the like. The suitable example may be an acid chloride; acid azide; a mixed acid anhydride with an acid such as substituted phosphoric acid (e.g., dialkylphosphoric acid, phenylphosphoric acid, diphenylphosphoric acid, dibenzylphosphoric acid, halogenated phosphoric acid, etc.), dialkylphosphorus acid, sulfurous acid, thiosulfuric acid, alkanesulfuric acid (e.g., methanesulfonic acid, ethanesulfonic acid, etc.), sulfuric acid, alkylcarbonic acid, aliphatic carboxylic acid (e.g., pivalic acid, pentanoic acid, isopentanoic acid, 2-ethylbutyric acid, trichloroacetic acid, etc.); aromatic carboxylic acid (e.g., benzoic acid, etc.); a symmetrical acid anhydride; an activated amide with imidazole, 4-substituted imidazole, dimethylpyrazole, triazole or tetrazole; an activated ester (e.g. cyanomethyl ester, methoxymethyl ester, dimethyliminomethyl [$(CH_3)_2{}^+N=CH-$] ester, vinyl ester, propargyl ester, p-nitrophenyl ester, 2,4-dinitrophenyl ester, trichlorophenyl ester, pentachlorophenyl ester, mesylphenyl ester, phenylazophenyl ester, phenylthio ester, p-nitrophenyl thioester, p-cresyl thioester, carboxymethyl thioester, pyranyl ester, pyridyl ester, piperidyl ester, 8-quinolyl thioester, etc.); an ester with a N-hydroxy compound (e.g., N,N-dimethylhydroxylamine, 1-hydroxy-2-(1H)-pyridone, N-hydroxysuccinimide, N-hydroxybenzotriazole, N-hydroxyphthalimide, 1-hydroxy-6-chloro-1H-benzotriazole, etc.); and the like. These reactive derivatives can optionally be selected from them according to the kind of the

compound (III) to be used.

This reaction is usually carried out in a solvent such as water, alcohol (e.g., methanol, ethanol, etc.), benzene, N,N-dimethylformamide, tetrahydrofuran, toluene, methylene chloride, ethylene dichloride, chloroform, dioxane, diethyl ether or any other solvents which do not adversely affect the reaction, or the mixture thereof.

The reaction temperature is not critical and the reaction is usually carried out under cooling to heating.

The reaction may be also carried out in the presence of an inorganic or an organic base such as an alkali metal (e.g., sodium, potassium, etc.), an alkali metal hydroxide (e.g., sodium hydroxide, potassium hydroxide, etc.), an alkali metal hydrogencarbonate (e.g., sodium hydrogencarbonate, potassium hydrogencarbonate, etc.), alkali metal carbonate (e.g., sodium carbonate, potassium carbonate, etc.), tri(lower)alkylamine (e.g., trimethylamine, triethylamine, diisopropylethylamine, etc.), alkali metal hydride (e.g., sodium hydride, etc.), alkali metal (lower)alkoxide (e.g., sodium methoxide, sodium ethoxide, etc.), pyridine, lutidine, picoline, dimethylaminopyridine, N-(lower)alkylmorpholine, N,N-di(lower)alkylbenzylamine, N,N-di(lower)alkylaniline or the like.

Process 2

The compound (Ib) or a salt thereof can be prepared by reacting the compound (IV) or its reactive derivative at the carboxy group or a salt thereof with the compound (V) or its reactive derivative at the amino group or a salt thereof.

This reaction can be carried out in a similar manner to that of the aforementioned Process 1, and therefore the reagents to be used and the reaction conditions (e.g., solvent, reaction temperature, etc.) can be referred to those of the Process 1.

Process 3

The compound (Ic) or a salt thereof can be prepared by reacting the compound (VI) or its reactive derivative at the hydroxy group or a salt thereof with the compound (VII) or a salt thereof.

This reaction is usually carried out in a solvent such as water, alcohol (e.g., methanol, ethanol, etc.), benzene, N,N-dimethylformamide, tetrahydrofuran, toluene, methylene chloride, ethylene dichloride, chloroform, dioxane, diethyl ether or any other solvents which do not adversely affect the reaction, or the mixture thereof.

The reaction temperature is not critical and the reaction is usually carried out under cooling to heating.

The reaction is usually carried out in the presence of an acid including Lewis acid.

Suitable acid may include an organic acid [e.g. formic acid, acetic acid, propionic acid, trichloroacetic acid, trifluoroacetic acid, etc.] and an inorganic acid [e.g. hydrochloric acid, hydrobromic acid, sulfuric acid, hydrogen chloride, hydrogen bromide, zinc halide (e.g., zinc chloride, zinc bromide, etc.), etc.] and the like.

The reaction may be also carried out in the presence of an inorganic or an organic base such as an alkali metal (e.g., sodium, potassium, etc.), an alkali metal hydroxide (e.g., sodium hydroxide, potassium hydroxide, etc.), an alkali metal hydrogencarbonate (e.g., sodium hydrogencarbonate, potassium hydrogencarbonate, etc.), alkali metal carbonate (e.g., sodium carbonate, potassium carbonate, etc.), tri(lower)alkylamine (e.g., trimethylamine, triethylamine, diisopropylethylamine, etc.), alkali metal hydride (e.g., sodium hydride, etc.), alkali metal (lower)alkoxide (e.g. sodium methoxide, sodium ethoxide, etc.), pyridine, lutidine, picoline, dimethylaminopyridine, N-(lower)alkylmorpholine, N,N-di(lower)alkylbenzylamine, N,N-di(lower)alkylaniline or the like.

When the base, the acid and/or the starting compound are in liquid, they can be used also as a solvent.

Process 4

The compound (Id) or a salt thereof can be prepared by reacting the compound (VIII) or a salt thereof with the compound (IX) or a salt thereof to Wittig Reaction.

This reaction is usually carried out in a solvent such as water, alcohol (e.g., methanol, ethanol, etc.), benzene, N,N-dimethylformamide, dimethylsulfoxide, nitromethane, tetrahydrofuran, toluene, methylene chloride, ethylene-dichloride, chloroform, dioxane, diethyl ether or any other solvents which do not adversely affect the reaction, or the mixture thereof.

The reaction temperature is not critical and the reaction is usually carried out under cooling to heating.

The reaction may be also carried out in the presence of an inorganic or an organic base such as an alkali metal (e.g., sodium, potassium, etc.), an alkali metal hydroxide (e.g., sodium hydroxide, potassium hydroxide, etc.), an alkali metal hydrogencarbonate (e.g., sodium hydrogencarbonate, potassium hydrogencarbonate, etc.), alkali metal carbonate (e.g., sodium carbonate, potassium carbonate, etc.), tri(lower)alkylamine (e.g., trimethylamine, triethylamine, diisopropylethylamine, etc.), alkali metal hydride (e.g., sodium hydride, etc.), alkali metal (lower)alkoxide (e.g. sodium methoxide, sodium ethoxide, potassium t-butoxide, etc.), pyridine, lutidine, picoline, dimethylaminopyridine, N-(lower)alkylmorpholine, N,N-di(lower)alkylbenzylamine, N,N-di(lower)alkylaniline, methyllitium, n-butyllitium, phenyllitium, 1,5-diazabicyclo[4.3.0]non-5-ene, or the like.

When the base, the acid and/or the starting compound are in liquid, they can be used also as a solvent.

Process 5

The compound (Ie) or a salt thereof can be prepared by reacting the compound (X) or its reactive derivative at the amino group or a salt thereof with the compound (XI) or a salt thereof.

This reaction is usually carried out in a solvent such as water, alcohol (e.g., methanol, ethanol, etc.), benzene, N,N-dimethylformamide, tetrahydrofuran, toluene, methylene chloride, ethylene dichloride, chloroform, dioxane, diethyl ether or any other solvents which do not adversely affect the reaction, or the mixture thereof.

The reaction temperature is not critical and the reaction is usually carried out under cooling to heating.

The reaction is usually carried out in the presence of an acid including Lewis acid.

Suitable acid may include an organic acid [e.g. formic acid, acetic acid, propionic acid, trichloroacetic acid, trifluoroacetic acid, etc.] and an inorganic acid [e.g. hydrochloric acid, hydrobromic acid, sulfuric acid, hydrogen chloride, hydrogen bromide, zinc halide (e.g., zinc chloride, zinc bromide, etc.), etc.] and the like.

The reaction may be also carried out in the presence of an inorganic or an organic base such as an alkali metal (e.g., sodium, potassium, etc.), an alkali metal hydroxide (e.g., sodium hydroxide, potassium hydroxide, etc.), an alkali metal hydrogencarbonate (e.g., sodium hydrogencarbonate, potassium hydrogencarbonate, etc.), alkali metal carbonate (e.g., sodium carbonate, potassium carbonate, etc.), tri(lower)alkylamine (e.g., trimethylamine, triethylamine, diisopropylethylamine, etc.), alkali metal hydride (e.g., sodium hydride, etc.), alkali metal (lower)alkoxide (e.g., sodium methoxide, sodium ethoxide, etc.), pyridine, lutidine, picoline, dimethylaminopyridine, N-(lower)alkylmorpholine, N,N-di(lower)alkylbenzylamine, N,N-di(lower)alkylaniline or the like.

When the base, the acid and/or the starting compound are in liquid, they can be used also as a solvent.

Process 6

The compound (If) or a salt thereof can be prepared by reacting the compound (VI) or its reactive derivative at the hydroxy group or a salt thereof with the compound (XII) or its reactive derivative at the carboxy group or a salt thereof.

Suitable reactive derivative at the hydroxy group of the compound (VI) may include halide, sulfonate, sulfate, diazo compound, and the like.

Suitable reactive derivative at the carboxy group of the compound (XII) may include an acid halide, an acid anhydride, an activated ester, and the like. The suitable example may be an acid chloride; acid azide; a mixed acid anhydride with an acid such as substituted phosphoric acid (e.g., dialkylphosphoric acid, phenylphosphoric acid, diphenylphosphoric acid, dibenzylphosphoric acid, halogenated phosphoric acid, etc.), dialkylphosphorus acid, sulfurous acid, thiosulfuric acid, alkanesulfuric acid (e.g., methanesulfonic acid, ethanesulfonic acid, etc.), sulfuric acid, alkylcarbonic acid, aliphatic carboxylic acid (e.g., pivalic acid, pentanoic acid, isopentanoic acid, 2-ethylbutyric acid, trichloroacetic acid, etc.); aromatic carboxylic acid (e.g., benzoic acid, etc.); a symmetrical acid anhydride; an activated amide with imidazole, 4-substituted imidazole, dimethylpyrazole, triazole or tetrazole; an activated ester (e.g., cyanomethyl ester, methoxymethyl ester, dimethyliminomethyl [$(CH_3)_2{}^+N=CH-$] ester, vinyl ester, propargyl ester, p-nitrophenyl ester, 2,4-dinitrophenyl ester, trichlorophenyl ester, pentachlorophenyl ester, mesylphenyl ester, phenylazophenyl ester, phenylthio ester, p-nitrophenyl thioester, p-cresyl thioester, carboxymethyl thioester, pyranyl ester, pyridyl

ester, piperidyl ester, 8-quinolyl thioester, etc.); an ester with a N-hydroxy compound (e.g., N,N-dimethylhydroxylamine, 1-hydroxy-2-(1H)-pyridone, N-hydroxysuccinimide, N-hydroxybenzotriazole, N-hydroxyphthalimide, 1-hydroxy-6-chloro-1H-benzotriazole, etc.); and the like. These reaction derivatives can optionally be selected from them according to the kind of the compound (XII) to be used.

This reaction is usually carried out in the presence of a base.

Suitable base may include, for example, an inorganic base such as alkali metal hydroxide (e.g., sodium hydroxide, potassium hydroxide, etc.), alkaline earth metal hydroxide (e.g., magnesium hydroxide, calcium hydroxide, etc.), alkali metal carbonate (e.g., sodium carbonate, potassium carbonate, cesium carbonate, etc.), alkaline earth metal carbonate (e.g., magnesium carbonate, calcium carbonate, etc.), alkali metal bicarbonate (e.g., sodium bicarbonate, potassium bicarbonate, etc.), alkali metal acetate (e.g., sodium acetate, potassium acetate, etc.), alkaline earth metal phosphate (e.g., magnesium phosphate, calcium phosphate, etc.), alkali metal hydrogen phosphate, (e.g., disodium hydrogen phosphate, dipotassium hydrogen phosphate, etc.) or the like, and an organic base such as trialkylamine (e.g., trimethylamine, triethylamine, etc.), pyridine, piccline, N-methylpyrrolidine, N-methylmorpholine, 1,5-diazabicyclo[4.3.0]non-5-ene, 1,4-diazabicyclo[2.2.2]-octane, 1,5-diazabicyclo[5.4.0]undecene-5 or the like.

This reaction is usually carried out in a solvent such as benzene, N,N-dimethylformamide, tetrahydrofuran, toluene, methylene chloride, ethylene dichloride, chloroform or any other solvents which do not adversely affect the reaction, or the mixture thereof.

The reaction temperature is not critical and the reaction is usually carried out under cooling to heating.

Process 7

The object compound (Ih) or a salt thereof can be prepared by reacting a compound (Ig) or its reactive derivative at the carboxy group or a salt thereof with a compound (XIII) or its reactive derivative at the amino group or a salt thereof.

Suitable reactive derivative at the carboxy group of the compound (Ig) may include an acid halide, an acid anhydride, an activated amide, an activated ester, and the like. Suitable examples of the reactive derivatives may be an acid chloride; an acid azide; a mixed acid anhydride with an acid such as substituted phosphoric acid [e.g. dialkylphosphoric acid, phenylphosphoric acid, diphenylphosphoric acid, dibenzylphosphoric acid, halogenated phosphoric acid, etc.], dialkylphosphorous acid, sulfurous acid, thiosulfuric acid, sulfuric acid, sulfonic acid [e.g., methanesulfonic acid, etc.], aliphatic carboxylic acid [e.g., acetic acid, propionic acid, butyric acid, isobutyric acid, pivalic acid, pentanoic acid, isopentanoic acid, 2-ethylbutyric acid, trichloroacetic acid, etc.] or aromatic carboxylic acid [e.g., benzoic acid, etc.]; a symmetrical acid anhydride; an activated amide with imidazole, 4-substituted imidazole, dimethylpyrazole, triazole, tetrazole or 1-hydroxy-1H-benzotriazole; or an activated ester [e.g. cyanomethyl ester, methoxymethyl ester, dimethyliminomethyl [$(CH_3)_2\overset{+}{N}=CH-$] ester, vinyl ester, propargyl ester, p-nitrophenyl ester, 2,4-dinitrophenyl ester, trichlorophenyl ester, pentachlorophenyl ester, mesylphenyl ester, phenylazophenyl ester, phenyl thioester, p-nitrophenyl thioester, p-cresyl thioester, carboxymethyl thioester, pyranyl ester, pyridyl ester, piperidyl ester, 8-quinolyl thioester, etc.], or an ester with a N-hydroxy compound [e.g., N,N-dimethylhydroxyamine, 1-hydroxy-2-(1H)-pyridone, N-hydroxysuccinimide, N-hydroxyphthalimide, 1-hydroxy-1H-benzotriazole, etc.], and the like. These reactive derivatives can optionally be

selected from them according to the kind of the compound (Ig) to be used.

Suitable salts of the compound (Ig) and its reactive derivative can be referred to the ones as exemplified for the compound (I).

Suitable reactive derivative at the amino group of the compound (XIII) may include Schiff's base type imino or its tautomeric enamine type isomer formed by the reaction of the compound (XIII) with a carbonyl compound such as aldehyde, ketone or the like; a silyl derivative formed by the reaction of the compound (XIII) with a silyl compound such as bis(trimethylsilyl)acetamide, mono(trimethylsilyl)acetamide, bis(trimethylsilyl)urea or the like; a derivative formed by reaction of the compound (XIII) with phosphorus trichloride or phosgene, and the like.

Suitable salts of the compound (XIII) and its reactive derivative can be referred to the ones as exemplified for the compound (I).

The reaction is usually carried out in a conventional solvent such as water, alcohol [e.g., methanol, ethanol, etc.], acetone, dioxane, acetonitrile, chloroform, methylene chloride, ethylene chloride, tetrahydrofuran, ethyl acetate, N,N-dimethylformamide, pyridine or any other organic solvent which does not adversely influence the reaction. These conventional solvent may also be used in a mixture with water.

In this reaction, when the compound (Ig) is used in a free acid form or its salt form, the reaction is preferably carried out in the presence of a conventional condensing agent such as N,N'-dicyclohexylcarbodiimide;
N-cyclohexyl-N'-morpholinoethylcarbodiimide;
N-cyclohexyl-N'-(4-diethylaminocyclohexyl)carbodiimide;
N,N'-diethylcarbodiimide, N,N'-diisopropylcarbodiimide;
N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide;
N,N'-carbonylbis-(2-methylimidazole);

pentamethyleneketene-N-cyclohexylimine; diphenylketene-N-cyclohexylimine; ethoxyacetylene; 1-alkoxy-1-chloroethylene; trialkylphosphite; ethyl polyphosphate; isopropyl polyphosphate; phosphorous oxychloride (phosphoryl chloride); phosphorus trichloride; thionyl chloride; oxalyl chloride; lower alkyl haloformate [e.g. ethyl chloroformate, isopropyl chloroformate, etc.]; triphenylphosphine; 2-ethyl-7-hydroxybenzisoxazolium salt; 2-ethyl-5-(m-sulfophenyl)isoxazolium hydroxide intramolecular salt; 1-(p-chlorobenzenesulfonyloxy)-6-chloro-1H-benzotriazole; so-called Vilsmeier reagent prepared by the reaction of N,N-dimethylformamide with thionyl chloride, phosgene, trichloromethyl chloroformate, phosphorus oxychloride, methanesulfonyl chloride, etc.; or the like.

The reaction may also be carried out in the presence of an inorganic or organic base such as an alkali metal carbonate, alkali metal bicarbonate, tri(lower)alkylamine, pyridine, N-(lower)alkylmorpholine, N,N-di(lower)alkylbenzylamine, or the like.

The reaction temperature is not critical, and the reaction is usually carried out under cooling to warming.

Process 8

The compound (Ij) or a salt thereof can be prepared by reacting the compound (Ii) or a salt thereof with Grignard Reagent.

Suitable Grignard reagent to be used in the present reaction may include the compound of the formula :

$$R^{12} - MgX'' \qquad (XIV)$$

(wherein R^{12} is lower alkyl, and
X" is halogen.)

This reaction is usually carried out in a solvent such

as tetrahydrofuran, toluene, methylene chloride, ethylene dichloride, chloroform, dioxane, diethyl ether or any other solvent which do not adversely affect the reaction, or the mixture thereof.

The reaction temperature is not critical and the reaction is usually carried out under cooling to heating.

Process 9

The object compound (Iℓ) or a salt thereof can be prepared by subjecting a compound (Ik) or a salt thereof to de-acylation reaction of acylamino group.

This reaction is carried out in accordance with a conventional method such as hydrolysis, reduction or the like.

The hydrolysis is preferably carried out in the presence of a base or an acid including Lewis acid. Suitable base may include an inorganic base and an organic base such as an alkali metal [e.g., sodium, potassium, etc.], an alkaline earth metal [e.g., magnesium, calcium, etc.], the hydroxide or carbonate or bicarbonte thereof, trialkylamine [e.g., trimethylamine, triethylamine, etc.], picoline, 1,5-diazabicyclo[4.3.0]non-5-ene, 1,4-diazabicyclo[2.2.2]-octane, 1,8-diazabicyclo[5.4.0]undec-7-ene, or the like.

Suitable acid may include an organic acid [e.g., formic acid, acetic acid, propionic acid, trichloroacetic acid, trifluoroacetic acid, etc.] and an inorganic acid [e.g. hydrochloric acid, hydrobromic acid, sulfuric acid, hydrogen chloride, hydrogen bromide, etc.].

The elimination using Lewis acid such as trihaloacetic acid [e.g. trichloroacetic acid, trifluoroacetic acid, etc.] or the like is preferably carried out in the presence of cation trapping agents [e.g. anisole, phenol, etc.].

The reaction is usually carried out in a solvent such as water, an alcohol [e.g. methanol, ethanol, etc.], methylene

chloride, tetrahydrofuran, a mixture thereof or any other solvent which does not adversely influence the reaction. A liquid base or acid can be also used as the solvent. The reaction temperature is not critical and the reaction is usually carried out under cooling to warming.

The reduction method applicable for the elimination reaction may include chemical reduction and catalytic reduction.

Suitable reducing agents to be used in chemical reduction are a combination of metal [e.g., tin, zing, iron, etc.] or metallic compound [e.g., chromium chloride, chromium acetate, etc.] and an organic or inorganic acid [e.g., formic acid, acetic acid, propionic acid, trifluoroacetic acid, p-toluenesulfonic acid, hydrochloric acid, hydrobromic acid, etc.].

Suitable catalysts to be used in catalytic reduction are conventional ones such as platinum catalysts [e.g. platinum plate, spongy platinum, platinum black, colloidal platinum, platinum oxide, platinum wire, etc.], palladium catalysts [e.g., spongy palladium, palladium black, palladium oxide, palladium on carbon, colloidal palladium, palladium on barium, sulfate, palladium on barium carbonate, etc.], nickel catalysts [e.g., reduced nickel, nickel oxide, Raney nickel, etc.], cobalt catalysts [e.g. reduced cobalt, Raney cobalt, etc.], iron catalysts [e.g. reduced iron, Raney iron, etc.], copper catalysts [e.g. reduced copper, Raney copper, Ullman copper, etc.] and the like.

The reduction is usually carried out in a conventional solvent which does not adversely influence the reaction such as water, methanol, ethanol, propanol, N,N-dimethylformamide, or a mixture thereof. Additionally, in case that the above-mentioned acids to be used in chemical reduction are in liquid, they can also be used as a solvent. Further, a suitable solvent to be used in catalytic reduction may be the above-mentioned solvent, and other conventional solvent such

as diethyl ether, dioxane, tetrahydrofuran, etc., or a mixture thereof.

The reaction temperature of this reduction is not critical and the reaction is usually carried out under cooling to warming.

Process 10

The compound (Ik) or a salt thereof can be prepared by subjecting the compound (Iℓ) or its reactive derivative at the amino group, or a salt thereof to acylation reaction.

Suitable acylating agent to be used in the present acylation reaction may include the compound of the formula :

$$R^{13} - OH \qquad (XV)$$

(wherein R^{13} is acyl)

or its reactive derivative, or a salt thereof.

Suitable reactive derivative at the amino group of the compound (Iℓ) may include Schiff's base type imino or its tautomeric enamine type isomer formed by the reaction of the compound (Iℓ) with a carbonyl compound such as aldehyde, ketone or the like; a silyl derivative formed by the reaction of the compound (Iℓ) with a silyl compound such as N,O-bis(trimethylsilyl)acetamide, N-trimethylsilylacetamide or the like; a derivative formed by the reaction of the compound (Iℓ) with phosphorus trichloride or phosgene, and the like.

Suitable reactive derivative of the compound (XV) may include an acid halide, an acid anhydride, an activated ester, and the like. The suitable example may be an acid chloride; acid azide; a mixed acid anhydride with an acid such as substituted phosphoric acid (e.g., dialkylphosphoric acid, phenylphosphoric acid, diphenylphosphoric acid, dibenzylphosphoric acid, halogenated phosphoric acid, etc.),

dialkylphosphorous acid, sulfurous acid, thiosulfuric acid, alkanesulfonic acid (e.g., methanesulfonic acid, ethanesulfonic acid, etc.), sulfuric acid, alkylcarbonic acid, aliphatic carboxylic acid (e.g., pivalic acid, pentanoic acid, isopentanoic acid, 2-ethylbutyric acid, trichloroacetic acid, etc.); aromatic carboxylic acid (e.g., benzoic acid, etc.); a symmetrical acid anhydride; an activated amide with imidazole, 4-substituted imidazole, dimethylpyrazole, triazole or tetrazole; an activated ester (e.g., cyanomethyl, ester methoxymethyl ester, dimethyliminomethyl [$(CH_3)_2^+N=CH-$] ester, vinyl ester, propargyl ester, p-nitrophenyl ester, 2,4-dinitrophenyl ester, trichlorophenyl ester, pentachlorophenyl ester, mesylphenyl ester, phenylazophenyl ester, phenylthioester, p-nitrophenyl thioester, p-cresyl thioester, carboxymethyl thioester, pyranyl ester, pyridyl ester, piperidyl ester, 8-quinolyl thioester, etc.); an ester with a N-hydroxy compound (e.g., N,N-dimethylhydroxylamine, 1-hydroxy-2-(1H)-pyridone, N-hydroxysuccinimide, N-hydroxybenzotriazole, N-hydroxyphthalimide, 1-hydroxy-6-chloro-1H-benzotriazole, etc.); and the like. These reactive derivatives can optionally be selected from them according to the kind of the compound (XV) to be used.

The reaction is usually carried out in a conventional solvent such as water, acetone, dioxane, acetonitrile, chloroform, methylene chloride, ethylene chloride, tetrahydrofuran, ethyl acetate, N,N-dimethylformamide, pyridine or any other organic solvent which do not adversely affect the reaction, or the mixture thereof.

When the compound (XV) is used in free acid form or its salt form in the reaction, the reaction is preferably carried out in the presence of a conventional condensing agent such as N,N'-dicyclohexylcarbodiimide; N-cyclohexyl-N'-morpholinoethylcarbodiimide); N-cyclohexyl-N'-(4-diethylaminocyclohexyl)carbodiimide;

N,N'-diisopropylcarbodiimide;
N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide;
N,N-carbonylbis(2-methylimidazole);
pentamethyleneketene-N-cyclohexylimine;
diphenylketene-N-cyclohexylimine, ethoxyacetylene;
1-alkoxy-1-chloroethylene; trialkyl phosphite; isopropyl polyphosphate; phosphorous oxychloride (phosphoryl chloride);
phosphorous trichloride;
thionyl chloride; oxalyl chloride; triphenylphosphite;
2-ethyl-7-hydroxybenzisoxazolium salt; 2-ethyl-5-(m-sulfophenyl)isoxazolium hydroxide intra-molecular salt;
1-(p-chlorobenzenesulfonyloxy)-6-chloro-1H-benzotriazole;
so-called Vilsmeier reagent prepared by the reaction of N,N-dimethylformamide with thionyl chloride, phosgene, phosphorous oxychloride, etc.; or the like.

The reaction may also be carried out in the presence of an organic or inorganic base such as an alkali metal bicarbonate, tri(lower)alkylamine, pyridine, N-(lower)alkylmorphorine, N,N-di(lower)alkylbenzylamine, or the like.

The reaction temperature is not critical, and the reaction is usually carried out under cooling to heating.

Process 11

The compound (Im) or a salt thereof can be prepared by subjecting the compound (Ij) or a salt thereof to acylation reaction. This reaction can be carried out in a similar manner to that of the afore-mentioned Process 10, and therefore the reagents to be used and the reaction conditions (e.g., solvent, reaction temperature, etc.) can be referred to those of the Process 10.

Process 12

The compound (Io) or a salt thereof can be prepared by reacting the compound (In) or a salt thereof with lower

alkane substituted with oxo (XIV) or a salt thereof.

This reaction is usually carried out in a solvent such as water, alcohol (e.g., methanol, ethanol, etc.), benzene, N,N-dimethylformamide, tetrahydrofuran, toluene, methylene chloride, ethylene dichloride, chloroform, dioxane, diethyl ether or any other solvents which do not adversely affect the reaction, or the mixture thereof.

The reaction temperature is not critical and the reaction is usually carried out under cooling to heating.

The reaction is usually carried out in the presence of an acid including Lewis acid.

Suitable acid may include an organic acid [e.g. formic acid, acetic acid, propionic acid, trichloroacetic acid, trifluoroacetic acid, etc.] and an inorganic acid [e.g. hydrochloric acid, hydrobromic acid, sulfuric acid, hydrogen chloride, hydrogen bromide, zinc halide (e.g., zinc chloride, zinc bromide, etc.), etc.] and the like.

When the acid and/or the starting compound are in liquid, they can be used also as a solvent.

Process 13

The compound (Iq) or a salt thereof can be prepared by reacting the compound (Ip) or a salt thereof with the compound (XV) or a salt thereof.

This reaction can be carried out in a similar manner to that of the afore-mentioned Process 3, and therefore the reagents to be used and the reaction conditions (e.g., solvent, reaction temperature, etc.) can be referred to those of the Process 3.

The process for preparing the starting compound (IIa) is explained in detail in the following.

Process A

The compound (IIa) or a salt thereof can be prepared by

reacting the compound (XVI) or a salt thereof with the compound (XVII) or a salt thereof.

This reaction is usually carried out in a solvent such as water, alcohol (e.g., methanol, ethanol, etc.), benzene, N,N-dimethylformamide, tetrahydrofuran, toluene, methylene chloride, ethylene dichloride, chloroform, 1,2-dimethoxyethane, dioxane, diethyl ether or any other solvents which do not adversely affect the reaction, or the mixture thereof.

The reaction temperature is not critical and the reaction is usually carried out under cooling to heating.

The reaction is usually carried out in the presence of an inorganic or an organic base such as an alkali metal (e.g., sodium, potassium, etc.), an alkali metal hydroxide (e.g., sodium hydroxide, potassium hydroxide, etc.), an alkali metal hydrogencarbonate (e.g., sodium hydrogencarbonate, potassium hydrogencarbonate, etc.), alkali metal carbonate (e.g., sodium carbonate, potassium carbonate, etc.), tri(lower)alkylamine (e.g., trimethylamine, triethylamine, diisopropylethylamine, etc.), alkali metal hydride (e.g., sodium hydride, etc.), alkali metal (lower)alkoxide (e.g. sodium methoxide, sodium ethoxide, etc.), pyridine, lutidine, picoline, dimethylaminopyridine, N-(lower)alkylmorpholine, N,N-di(lower)alkylbenzylamine, N,N-di(lower)alkylaniline or the like.

When the base and/or the starting compound are in liquid, they can be used also as a solvent.

Among the starting compounds (II) to (XVI), some of them are novel compounds. They can be prepared by the similar manners to those disclosed in Preparations 1 and 2 mentioned later in the present specification, or any process known in this field of the art for preparing structurally analogous compounds thereto.

The object compound (I) can be prepared by any process

known in this field of the art except the above Processes 1 to 13 and Process A.

The compounds obtained by the above Processes 1 to 13 and Process A can be isolated and purified by a conventional method such as pulverization, recrystallization, columnchromatography, reprecipitation or the like.

It is to be noted that each of the object compound (I) may include one or more stereoisomer such as optical isomer(s) and geometrical isomer(s) due to asymmetric carbon atom(s) and double bond(s) and all such isomers and mixture thereof are included within the scope of this invention.

The pharmaceutical composition of the present invention can be used in the form of a pharmaceutical preparation, for example, in solid, semisolid or liquid form, which contains the object compound (I) or a pharmaceutically acceptable salt thereof, as an active ingredient in admixture with an organic or inorganic carrier or excipient which is suitable for rectal; pulmonary (nasal or buccal inhalation); ocular; external (topical); oral administration; parenteral (including subcutaneous, intravenous and intramuscular) administrations; insufflation (including aerosols from metered dose inhalator); nebulizer; or dry powder inhalator.

The active ingredient may be compounded, for example, with the usual non-toxic, pharmaceutically acceptable carriers in a solid form such as granules, tablets, dragees, pellets, troches, capsules, or suppositories; creams; ointments; aerosols; powders for insufflation; in a liquid form such as solutions, emulsions, or suspensions for injection; ingestion; eye drops; and any other form suitable for use. And, if necessary, there may be included in the above preparation auxiliary substance such as stabilizing, thickening, wetting, emulsifying and coloring agents; perfumes or buffer; or any other commonly may be used as additives.

The object compound (I) or a pharmaceutically acceptable

salt thereof include solvated compound [e.g., enclosure compound (e.g., hydrate, etc.)].

The object compound (I) or a pharmaceutically acceptable salt thereof include both its crystal form and non-crystal form.

The object compound (I) or a pharmaceutically acceptable salt thereof is/are included in the pharmaceutical composition in an amount sufficient to produce the desired effect upon the process or condition of diseases.

The pharmaceutical composition of the present invention can be manufactured by the conventional method in this field of the art. If necessary, the technique generally used in this field of the art for improving the bioavailability of a drug can be applied to the pharmaceutical composition of the present invention.

While the dosage of therapeutically effective amount of the object compound (I) varies from and also depends upon the age and condition of each individual patient to be treated, in the case of intravenous administration, a daily dose of 0.001-100 mg of the object compound (I) per kg weight of a human being or an animal, in the case of intramuscular administration, a daily dose of 0.001-100 mg of the object compound (I) per kg weight of a human being of an animal, in case of oral administration, a daily dose of 0.001-200 mg of the object compound (I) per kg weight of a human being or an animal is generally given for the prevention and/or the treatment of aforesaid diseases 1 to 4 times a day in a human being or an animal.

In order to illustrate the usefulness of the object compound (I), the pharmacological test data of the representative compound of the compounds (I) is shown in the following.

Test Compound

(1) 8-(2,6-Dichlorobenzoylamino)-3-hydroxymethyl-2-trifluoromethyl-imidazo[1,2-a]pyridine hydrochloride

Test (Bone organ culture) :

Tesr Method

Calvariae from Wistar rats were excised and cultured in wells of 12-well culture plates containing 2 ml of Dulbecco's modified minimum essential medium supplemented with 10% fetal bovine serum and 10^{-8}M human parathyroid hormone fragment (1-34) [PTH] in the presence of the test compound. In control dishes, PTH was not added. Control and PTH control were exposed to an equivalent concentration of the vehicle. Six days later, the concentration of calcium in the medium was measured by methylxylenol blue method and the percentage of inhibition of PTH-induced bone resorption was calculated according to following formula.

$$\text{Inhibition (\%)} = \frac{\text{[Ca] in PTH control dishes} - \text{[Ca] in the test compound dishes}}{\text{[Ca] in PTH control dishes} - \text{[Ca] in control dishes}} \times 100$$

Test Result

Compound dose = 1×10^{-5} (M)

Test Compound	Inhibition (%)
(1)	100

The following Preparations and Examples are given for the purpose of illustrating the present invention in more detail.

Preparation 1

A solution of 2,3-diaminopyridine (6.27 g) and 1-chloro-3,3,3-trifluoroacetone (8.4 g) in ethanol (110 ml) was refluxed for 20 hours. The reaction mixture was evaporated in vacuo, and the residue was partitioned between ethyl acetate and aqueous saturated sodium bicarbonate. The organic layer was separated, dried over sodium sulfate, and evaporated in vacuo. The residue was purified by column chromatography on silica gel and the obtained solid was collected with diisopropyl ether to give 8-amino-2-trifluoromethylimidazo[1,2-a]pyridine (3.09 g).

NMR ($CDCl_3$, δ): 4.62 (2H, br s), 6.40 (1H, d, J=7.5Hz), 6.71 (1H, t, J=7.5Hz), 7.58 (1H, d, J=7.5Hz), 7.81 (1H, s)

FAB-Mass: 202 $(M+H)^+$

Preparation 2

A mixture of 2,3-diaminopyridine (2.18 g), ethyl 3-chloro-4-oxovalerate (2.88 g) and sodium bicarbonate (1.68 g) in 1,2-dimethoxyethane (40 ml) was stirred at 50°C for 30 minutes and then, refluxed for 6 hours. After separation of the insoluble matter by decantation and evaporation in vacuo, the residue was partitioned between ethyl acetate and aqueous saturated sodium bicarbonate. The organic layer was separated, washed with aqueous saturated sodium bicarbonate and brine, dried over sodium sulfate, and evaporated in vacuo. The residue was purified by column chromatography on silica gel. 4N Hydrogen chloride in ethyl acetate was added to the obtained solid and the solution was evaporated in vacuo. The residue was crystallized from ethanol to give 8-amino-3-ethoxycarbonylmethyl-2-methylimidazo[1,2-a]pyridine hydrochloride (899 mg).

mp : 222-223°C

NMR (DMSO-d_6, δ) : 1.20 (3H, t, J=7Hz), 2.45 (3H, s), 4.11 (2H, q, J=7Hz), 4.24 (2H, s), 6.57 (2H, br s),

6.90 (1H, d, J=8Hz), 7.20 (1H, t, J=8Hz), 7.92 (1H, d, J=8Hz)

Preparation 3

A mixture of 2,3-diaminopyridine (436 mg) and 1-bromo-3,3-dimethyl-2-butanone (836 mg) in ethanol (5 ml) was refluxed for 20 hours. The reaction mixture was cooled and the separated solid was collected and washed with ethanol to give 8-amino-2-(1,1-dimethylethyl)imidazo[1,2-a]pyridine hydrobromide (830 mg).

mp : >250°C

NMR ($CDCl_3$:CD_3OD = 1:1, δ) : 1.53 (9H, s), 6.98 (1H, d, J=7Hz), 7.12 (1H, t, J=7Hz), 7.62 (1H, s), 7.87 (1H, d, J=7Hz)

The following compounds (Preparations 4 to 14) were obtained according to a similar manner to that of Preparation 1.

Preparation 4

8-Amino-2-(2,2-dimethylpropyl)imidazo[1,2-a]pyridine

NMR ($CDCl_3$, δ) : 1.00 (9H, s), 2.65 (2H, s), 4.49 (2H, br s), 6.27 (1H, d, J=7Hz), 6.54 (1H, t, J=7Hz), 7.27 (1H, s), 7.53 (1H, d, J=7Hz)

Preparation 5

8-Amino-2-ethylimidazo[1,2-a]pyridine

NMR ($CDCl_3$, δ) : 1.34 (3H, t, J=7.5Hz), 2.82 (2H, q), 4.42 (2H, br s), 6.28 (1H, dd, J=7.5Hz and 1.0Hz), 6.53 (1H, t, J=7.5Hz), 7.27 (1H, s), 7.52 (1H, dd, J=7.5Hz and 1.0Hz)

Preparation 6

8-Aminoimidazo[1,2-a]pyridine

NMR ($CDCl_3$, δ) : 4.52 (2H, br s), 6.31 (1H, d, J=7Hz),

6.61 (1H, t, J=7Hz), 7.52 (2H, s), 7.60 (1H, d, J=7Hz)

Preparation 7

8-Amino-2-phenylimidazo[1,2-a]pyridine

mp : 138-139°C

Preparation 8

8-Amino-2-methyl-3-benzylimidazo[1,2-a]pyridine

mp : >250°C

NMR ($CDCl_3$, δ) : 2.50 (3H, s), 4.21 (2H, s), 4.43 (2H, br s), 6.29 (1H, d, J=7Hz), 6.50 (1H, t, J=7Hz), 7.05-7.35 (6H, m)

Preparation 9

8-Amino-3-ethoxycarbonyl-2-methylimidazo[1,2-a]pyridine

NMR ($CDCl_3$, δ) : 1.43 (3H, t, J=7Hz), 2.71 (3H, s), 4.42 (2H, q, J=7Hz), 4.48 (2H, br s), 6.55 (1H, d, J=7Hz), 6.78 (1H, t, J=7Hz), 8.72 (1H, d, J=7Hz)

Preparation 10

8-Amino-2-ethoxycarbonylimidazo[1,2-a]pyridine

NMR ($CDCl_3$, δ) : 1.43 (3H, t, J=7.5Hz), 4.47 (2H, q, J=7.5Hz), 4.68 (2H, br s), 6.32 (1H, d, J=7.5Hz), 6.68 (1H, t, J=7.5Hz), 7.57 (1H, d, J=7.5Hz), 8.10 (1H, s)

Preparation 11

8-Amino-3-ethoxycarbonyl-2-trifluoromethylimidazo-[1,2-a]pyridine

oil

NMR ($CDCl_3$, δ) : 1.35 (3H, t, J=7Hz), 4.34 (2H, q, J=7Hz), 6.62 (1H, d, J=7Hz), 6.95 (1H, t, J=7Hz), 8.80 (1H, d, J=7Hz)

Preparation 12

3-Acetyl-8-amino-2-methylimidazo[1,2-a]pyridine

mp : 191-193°C

NMR ($CDCl_3$, δ) : 2.61 (3H, s), 2.79 (3H, s), 4.50 (2H, m), 6.62 (1H, d, J=8Hz), 6.83 (1H, t, J=8Hz), 9.16 (1H, d, J=8Hz)

Preparation 13

8-Amino-3-methoxy-2-methylimidazo[1,2-a]]pyridine

mp : 120-122°C

NMR ($CDCl_3$, δ) : 2.42 (3H, s), 3.96 (3H, s), 4.39 (2H, br s), 6.23 (1H, d, J=8Hz), 6.59 (1H, t, J=8Hz), 7.38 (1H, d, J=8Hz)

Preparation 14

8-Amino-2-ethoxycarbonyl-3-methylimidazo[1,2-a]pyridine

mp : 146-147°C

NMR ($CDCl_3$, δ) : 1.46 (3H, t, J=7Hz), 2.77 (3H, s), 4.49 (2H, q, J=7Hz), 4.58-4.70 (2H, m), 6.34 (1H, d, J=8Hz), 6.73 (1H, t, J=8Hz), 7.38 (1H, d, J=8Hz)

Preparation 15

To a suspension of 2,3-diaminopyridine (1.09 g) in 1,2-dimethoxyethane (11 ml) was added 3-bromo-1,1,1-trifluoroacetone (1.09 ml) dropwise at 4°C. The mixture was stirred at 4°C for 15 minutes and at ambient temperature for 2 hours. To the reaction mixture was added ethyl acetate (11 ml) and the mixture was stirred at ambient temperature for 2 hours. The separated solid was collected and washed with ethyl acetate to give 3-amino-1,2-dihydro-2-imino-1-(2-oxo-3,3,3-trifluoropropyl)pyridine hydrobromide (2.786 g).

mp : 155-166°C

NMR (DMSO-d_6, δ) : 4.83 (1H, d, J=15Hz), 5.17 (1H, d, J=15Hz), 6.40 (2H, br s), 7.04 (1H, t, J=7Hz), 7.25 (1H, d, J=7Hz), 7.65 (1H, d, J=7Hz), 8.70 (1H, s)

Preparation 16

A solution of 3-amino-1,2-dihydro-2-imino-1-(2-oxo-3,3,3-trifluoropropyl)pyridine hydrobromide (2.75 g) in water (11 ml) was stirred at 90°C for 2 hours. The reaction mixture was cooled and to the mixture was added a solution of potassium carbonate (750 mg) in water (2.5 ml) dropwise. The mixture was stirred at ambient temperature for 1 hour and the separated solid was collected, washed with water and dried to give 8-amino-2-trifluoromethylimidazo[1,2-a]pyridine (1.545 g).

mp : 101-103°C

NMR ($CDCl_3$, δ) : 4.62 (2H, br s), 6.40 (1H, d, J=7.5Hz), 6.71 (1H, t, J=7.5Hz), 7.58 (1H, d, J=7.5Hz), 7.81 (1H, s)

Preparation 17

A mixture of 8-chloro-2-methylimidazo[1,2-a]pyrazine (120 mg) and 3M solution of ammonia in methanol (5 ml) was heated in a sealed tube at 120°C for 3 days. The reaction mixture was cooled and evaporated in vacuo. The solid residue was purified by flash column chromatography on silica gel and the obtained crystalline residue was triturated with diisopropyl ether to give 8-amino-2-methylimidazo[1,2-a]-pyrazine (55 mg).

NMR ($CDCl_3$, δ) : 2.44 (3H, s), 5.40 (2H, br s), 7.23-7.29 (2H, m), 7.43 (1H, d, J=5Hz)

ESI-MASS (M^++1) = 149

Preparation 18

A mixture of 3-acetyl-8-amino-2-methylimidazo[1,2-a]-pyridine (1.00 g), acetic anhydride (700 mg), and acetic acid (0.5 ml) in methylenechloride (10 ml) was stirred for 30 minutes at ambient temperature. After concentration in vacuo, the residue was partitioned between chloroform and aqueous saturated sodium bicarbonate. The separated organic

layer was dried over sodium sulfate and evaporated in vacuo. The obtained crude solid was triturated with diisopropyl ether to give 3-acetyl-8-acetylamino-2-methylimidazo[1,2-a]-pyridine (1.18 g).

mp : 174-175°C

NMR ($CDCl_3$, δ) : 2.31 (3H, s), 2.62 (3H, s), 2.79 (3H, s), 7.00 (1H, t, J=8Hz), 8.40 (1H, d, J=8Hz), 8.53 (1H, m), 9.37 (1H, d, J=8Hz)

Preparation 19

A mixture of 8-acetylamino-3-(1-hydroxy-1-methylethyl)-2-methylimidazo[1,2-a]pyridine (929 mg) and aqueous 3N-sodium hydroxide (4 ml) in ethanol (9 ml) was stirred for 4 hours at 80°C. The mixture was extracted with methylene chloride and the extract was dried over sodium sulfate and evaporated in vacuo. The obtained oil was crystallized from diisopropyl ether to give 8-amino-3-(1-hydroxy-1-methylethyl)-2-methylimidazo[1,2-a]pyridine (706 mg).

mp : 175-177°C

NMR ($CDCl_3$, δ) : 1.73 (6H, s), 2.41 (3H, s), 2.70 (1H, m), 4.38 (2H, m), 6.28 (1H, d, J=8Hz), 6.51 (1H, t, J=8Hz), 8.20 (1H, d, J=8Hz)

The following compound was obtained according to a similar manner to that of Preparation 19.

Preparation 20

3-Bromo-8-carboxy-2-methylimidazo[1,2-a]pyridine

mp : 191-195°C

NMR (DMSO-d_6, δ) : 2.41 (3H, s), 7.20 (1H, t, J=7Hz), 7.98 (1H, d, J=7Hz), 8.52 (1H, d, J=7Hz)

Preparation 21

N-Bromosuccinimide (3.74 g) was added to a solution of 8-ethoxycarbonyl-2-methylimidazo[1,2-a]pyridine (4.243 g) in

ethanol (40 ml). After stirring at ambient temperature for 30 minutes, the mixture was evaporated in vacuo and the residue was dissolved in dichloromethane. The solution was washed with aqueous saturated sodium bicarbonate and brine, dried over magnesium sulfate and evaporated in vacuo. The crystalline residue was recrystallized from diisopropyl ether to give 3-bromo-8-ethoxycarbonyl-2-methylimidazo[1,2-a]-pyridine (5.1 g).

mp : 76-78°C

NMR ($CDCl_3$, δ) : 1.44 (3H, t, J=7Hz), 2.56 (3H, s), 4.50 (2H, q, J=7Hz), 6.98 (1H, t, J=7Hz), 7.96 (1H, d, J=7Hz), 8.23 (1H, d, J=7Hz)

Preparation 22

A solution of methylmagnesium bromide in tetrahydrofuran (0.96M, 5.74 ml) was added to a solution of 3-acetyl-8-acetylamino-2-methylimidazo[1,2-a]pyridine (510 mg) in tetrahydrofuran (10 ml) dropwise with ice-cooling. The mixture was stirred at ambient temperature for 1 hour and to the mixture was added methylmagnesium bromide (2.3 ml). The mixture was stirred for 2 hours, quenched with aqueous saturated ammonium chloride and partitioned between ethyl acetate and water. The organic layer was separated, washed with brine, dried over sodium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel to give 8-acetylamino-3-(1-hydroxy-1-methylethyl)-2-methylimidazo[1,2-a]pyridine (amorphous).

NMR ($CDCl_3$, δ) : 1.76 (6H, s), 2.28 (3H, s), 2.43 (3H, s), 2.63 (1H, m), 6.70 (1H, t, J=8Hz), 8.06 (1H, d, J=8Hz), 8.48 (1H, d, J=8Hz), 8.60 (1H, m)

Example 1

2,6-Dichlorobenzoyl chloride (2.51 g) was added to a solution of 8-amino-2-trifluoromethylimidazo[1,2-a]pyridine (2.01 g) and triethylamine (1.31 g) in dichloromethane (30 ml). The mixture was stirred at ambient temperature for 1 hour and refluxed overnight. The mixture was diluted with dichloromethane, washed with aqueous saturated sodium bicarbonate and water, dried over sodium sulfate, and evaporated in vacuo. The residue was purified by column chromatography on silica gel and the obtained oil was crystallized from diisopropyl ether to give 8-(2,6-dichlorobenzoylamino)-2-trifluoromethylimidazo[1,2-a]pyridine (750 mg).

mp: 190-195°C

NMR ($CDCl_3$, δ): 6.99 (1H, t, J=7.5Hz), 7.32-7.44 (3H, m), 7.92 (1H, s), 7.95 (1H, d, J=7.5Hz), 8.52 (1H, dd, J=7.5 and 1.5Hz), 8.75 (1H, br s)

The following compound was obtained according to a similar manner to that of Example 1.

Example 2

8-(2,6-Dichlorobenzoylamino)-2-methylimidazo[1,2-a]-pyridine

mp : 197-198°C

NMR ($CDCl_3$, δ) : 2.42 (3H, s), 6.79 (1H, t, J=7Hz), 7.30-7.40 (4H, m), 7.83 (1H, d, J=7Hz), 8.33 (1H, d, J=7Hz), 8.70 (1H, br s)

Example 3

A mixture of 8-amino-3-ethoxycarbonylmethyl-2-methylimidazo[1,2-a]pyridine hydrochloride (890 mg), 2,6-dichlorobenzoyl chloride (760 mg) and N-methylmorpholine (833 mg) in N,N-dimethylacetamide (5 ml) was stirred at 60°C for 3 hours. The mixture was partitioned between ethyl acetate and

water. The organic layer was separated, washed with water and brine, dried over sodium sulfate, and evaporated in vacuo. The residue was purified by column chromatography on silica gel and the obtained solid was collected with ethanol to give 8-(2,6-dichlorobenzoylamino)-3-ethoxycarbonylmethyl-2-methylimidazo[1,2-a]pyridine (805 mg).

mp : 168-170°C

NMR ($CDCl_3$, δ) : 1.26 (3H, t, J=7Hz), 2.42 (3H, s), 3.87 (2H, s), 4.18 (2H, q, J=7Hz), 6.88 (1H, t, J=8Hz), 7.30-7.40 (3H, m), 7.80 (1H, d, J=8Hz), 8.38 (1H, d, J=8Hz), 8.75 (1H, br s)

Example 4

37% Hydrochloric acid (0.25 ml) was added to a solution of 8-(2,6-dichlorobenzoylamino)-2-trifluoromethylimidazo[1,2-a]pyridine (150 g) and formaldehyde 37% solution in water (0.5 ml) in acetic acid (2 ml). The mixture was stirred at 85°C for 20 hours and evaporated in vacuo. The residue was partitioned between ethyl acetate and aqueous saturated sodium bicarbonate. The organic layer was separated, washed with brine, dried over sodium sulfate, and evaporated in vacuo. The residue was purified by column chromatography on silica gel, and the obtained oil was crystallized from a mixture of diethyl ether and n-hexane to give 8-(2,6-dichlorobenzoylamino)-3-hydroxymethyl-2-trifluoromethylimidazo[1,2-a]pyridine (82 mg).

mp: 215-219°C

NMR ($CDCl_3$, δ): 2.26 (1H, t, J=7Hz), 5.10 (2H, d, J=7Hz), 7.04 (1H, t, J=7Hz), 7.27-7.40 (3H, m), 8.10 (1H, d, J=7Hz), 8.56 (1H, d, J=7Hz), 8.79 (1H, br s)

Example 5

A mixture of 8-(2,6-dichlorobenzoylamino)-2-methylimidazo[1,2-a]pyridine (50 mg), dimethylamine

hydrochloride (15 mg) and 37% formalin (19 mg) in acetic acid (1 ml) was stirred at 60°C for 1 hour. The mixture was evaporated in vacuo and the residue was partitioned between dichloromethane and aqueous saturated sodium bicarbonate. The organic layer was separated, dried over sodium sulfate and evaporated in vacuo. The residue was crystallized from diisopropyl ether to give 8-(2,6-dichlorobenzoylamino)-3-dimethylaminomethyl-2-methylimidazo[1,2-a]pyridine (38 mg).

mp : 173-175°C

NMR ($CDCl_3$, δ) : 2.26 (6H, s), 2.40 (3H, s), 3.67 (2H, s), 6.86 (1H, t, J=8Hz), 7.30-7.41 (3H, m), 8.01 (1H, d, J=8Hz), 8.49 (1H, d, J=8Hz), 8.78 (1H, br s)

Example 6

Methyl iodide (354 mg) was added to a solution of 8-(2,6-dichlorobenzoylamino)-3-dimethylaminomethyl-2-methylimidazo[1,2-a]pyridine (940 mg) in a mixture of acetone (30 ml) and tetrahydrofuran (10 ml) at 4°C. The solution was stirred at ambient temperature for 6 hours and evaporated in vacuo. The residual solid was triturated with ethyl acetate to give [[8-(2,6-dichlorobenzoylamino)-2-methylimidazo-[1,2-a]pyridin-3-yl]methyl]trimethylammonium iodide (1.37 g).

NMR (DMSO-d_6, δ) : 2.48 (3H, s), 3.10 (9H, s), 4.97 (2H, s), 7.09 (1H, t, J=8Hz), 7.44-7.56 (3H, m), 8.24 (1H, d, J=8Hz), 8.56 (1H, d, J=8Hz)

Example 7

In aqueous sodium hydroxide (2.08 ml) was added to a solution of 8-(2,6-dichlorobenzoylamino)-3-ethoxycarbonylmethyl-2-methylimidazo[1,2-a]pyridine (705 mg) in a mixture of tetrahydrofuran (4 ml) and methanol (4 ml). After stirring at ambient temperature for 3 hours, the organic solvent was evaporated in vacuo. The aqueous residue was neutralized with 1N-hydrochloric acid. The separated

solid was collected and washed with water and ethyl acetate to give 3-carboxymethyl-8-(2,6-dichlorobenzoylamino)-2-methylimidazo[1,2-a]pyridine (656 mg).

mp : >250°C

NMR (DMSO-d_6, δ) : 2.32 (3H, s), 4.00 (2H, s), 6.90 (1H, t, J=8Hz), 7.44-7.55 (3H, m), 8.03-8.08 (2H, m)

Example 8

A mixture of [[8-(2,6-dichlorobenzoylamino)-2-methylimidazo[1,2-a]pyridin-3-yl]methyl]trimethylammonium iodide (300 mg) and imidazole (197 mg) in ethanol (3 ml) was refluxed for 4 hours. The reaction mixture was evaporated in vacuo and the residue was partitioned between dichloromethane and aqueous saturated sodium bicarbonate. The organic layer was separated, washed with brine, dried over sodium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel and the obtained oil was crystallized from diisopropyl alcohol to give 8-(2,6-dichlorobenzoylamino)-3-(imidazol-1-yl)methyl-2-methylimidazo[1,2-a]pyridine (99 mg).

mp : 249-251°C

NMR ($CDCl_3$, δ) : 2.51 (3H, s), 5.40 (2H, s), 6.83-6.90 (2H, m), 7.10 (1H, s), 7.30-7.41 (3H, m), 7.46-7.53 (2H, m), 8.42 (1H, d, J=8Hz), 8.70 (1H, br s)

Example 9

To a mixture of 8-(2,6-dichlorobenzoylamino)-3-hydroxymethyl-2-trifluoromethylimidazo[1,2-a]pyridine hydrochloride (177 mg) and thionyl chloride (0.06 ml) in dichloromethane was added pyridine (1 drop). The mixture was stirred at ambient temperature for 30 minutes and evaporated in vacuo. The residue was partitioned between dichloromethane and aqueous saturated sodium bicarbonate. The organic layer was separated, dried over sodium sulfate

and evaporated in vacuo. The residue was dissolved in N,N-dimethylformamide (2 ml) and to the solution was added potassium carbonate (111 mg) and 2-mercaptoimidazole (60 mg). The mixture was stirred at ambient temperature for 1 hour and poured into a mixture of ice and water. The separated oil was extracted with ethyl acetate and the extract was washed with brine, dried over sodium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel and the obtained oil was crystallized from diisopropyl ether to give 8-(2,6-dichlorobenzoylamino)-3-(imidazol-2-yl)thiomethyl-2-trifluoromethylimidazo[1,2-a]-pyridine (170 mg).

mp : 218-220°C

NMR (DMSO-d_6, δ) : 4.63 (2H, s), 6.85-7.20 (2H, br), 7.17 (1H, t, J=8Hz), 7.43-7.58 (3H, m), 8.27 (1H, d, J=8Hz), 8.30 (1H, d, J=8Hz)

Example 10

1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (91 mg) and 1-hydroxybenzotriazole (64 mg) were added to a suspension of 3-carboxymethyl-8-(2,6-dichlorobenzoylamino)-2-methylimidazo[1,2-a]pyridine (150 mg) in N,N-dimethylformamide (1.5 ml), and the mixture was stirred at ambient temperature for 30 minutes. 2-Methoxy-ethylamine (36 mg) was added to the mixture, and the mixture was stirred at ambient temperature overnight. The mixture was partitioned between ethyl acetate and water, and the organic layer was separated. The aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with water and brine, dried over sodium sulfate, and evaporated in vacuo. The residue was purified by column chromatography on silica gel. 10% Methanolic hydrogen chloride (3 ml) was added to the obtained solid and the solution was evaporated in vacuo. The residue was crystallized from a mixture of ethanol and diethyl ether to

give 8-(2,6-dichlorobenzoylamino)-3-[N-(2-methoxyethyl)carbamoyl]methyl-2-methylimidazo[1,2-a]pyridine hydrochloride (119 mg).

mp : 227-231°C

NMR (DMSO-d_6, δ) : 2.47 (3H, s), 3.19-3.27 (5H, m), 3.30-3.38 (2H, m), 4.03 (2H, s), 7.43-7.65 (4H, m), 8.38 (1H, t, J=8Hz), 8.52 (1H, d, J=8Hz), 8.62 (1H, d, J=8Hz)

The following compound was obtained according to a similar manner to that of Example 10.

Example 11

8-(2,6-Dichlorobenzoylamino)-3-[[N-(3-methoxypropyl)-carbamoyl]methyl]-2-methylimidazo[1,2-a]pyridine hydrochloride

mp : 150-160°C

NMR (DMSO-d_6, δ) : 1.59-1.69 (2H, m), 2.48 (3H, s), 3.10 (2H, q, J=7Hz), 3.20 (3H, s), 3.31 (2H, t, J=7Hz), 4.00 (2H, s), 7.42-7.65 (4H, m), 8.24 (1H, t, J=7Hz), 8.52 (1H, d, J=8Hz), 8.60 (1H, d, J=8Hz)

Example 12

4N Hydrogen chloride in ethyl acetate (0.1 ml) was added to a solution of 8-(2,6-dichlorobenzoylamino)-3-hydroxymethyl-2-trifluoromethylimidazo[1,2-a]pyridine (100 mg) in ethyl acetate (3 ml). The separated solid was collected and washed with ethyl acetate to give 8-(2,6-dichlorobenzoylamino)-3-hydroxymethyl-2-trifluoromethyl-imidazo[1,2-a]pyridine hydrochloride (87 mg).

mp: 175-177°C

NMR ($CDCl_3$:CD_3OD=9:1, δ): 4.99 (2H, s), 7.20 (1H, t, J=7Hz), 7.25-7.40 (3H, m), 8.27 (1H, d, J=7Hz), 8.30 (1H, d, J=7Hz)

The following compounds (Example 13 to 14) were obtained according to a similar manner to that of Example 12.

Example 13

8-(2,6-dichlorobenzoylamino)-3-hydroxymethyl-2-trifluoromethyl-imidazo[1,2-a]pyridine methanesulfonate.

mp : 166-168°C

NMR (DMSO-d_6, δ) : 2.39 (3H, s), 4.93 (2H, s), 7.18 (1H, t, J=8Hz), 7.45-7.58 (3H, m), 8.29 (1H, d, J=8Hz), 8.35 (1H, d, J=8Hz)

Example 14

8-(2,6-Dichlorobenzoylamino)-3-(imidazol-2-yl)thiomethyl-2-trifluoromethylimidazo[1,2-a]pyridine hydrochloride

mp : >250°C

NMR (DMSO-d_6, δ) : 4.85 (2H, s), 7.28 (1H, t, J=8Hz), 7.43-7.58 (3H, m), 7.74 (2H, s), 8.39 (1H, d, J=8Hz), 8.56 (1H, d, J=8Hz)

Example 15

A mixture of [[8-(2,6-dichlorobenzoylamino)-2-methylimidazo[1,2-a]pyridin-3-yl]methyl]trimethylammonium iodide (600 mg) and imidazole (394 mg) in 2-propanol (6 ml) was refluxed for 1.5 hours. The reaction mixture was evaporated in vacuo and the residue was partitioned between dichloromethane and aqueous saturated sodium bicarbonate. The organic layer was separated, dried over sodium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel and the obtained oil was dissolved in 10% methanolic hydrogen chloride (2 ml). The solution was evaporated in vacuo and the residue was crystallized from ethanol to give 8-(2,6-dichlorobenzoylamino)-3-(imidazol-1-yl)methyl-2-methylimidazo[1,2-a]pyridine dihydrochloride (338 mg).

mp : 262°C (dec.)

NMR (DMSO-d_6, δ) : 2.60 (3H, s), 6.00 (2H, s), 7.39 (1H, m), 7.49-7.61 (3H, m), 7.72 (1H, s), 7.78 (1H, s), 8.54-8.67 (2H, m), 9.21 (1H, s)

The following compounds (Examples 16 to 51) were obtained according to a similar manner to that of Example 2.

Example 16

8-(2,6-Dichlorobenzoylamino)-2-(1,1-dimethylethyl)-imidazo[1,2-a]pyridine

mp : 232-233°C

NMR ($CDCl_3$, δ) : 1.38 (9H, s), 6.76 (1H, t, J=7Hz), 7.30-7.45 (4H, m), 7.82 (1H, d, J=7Hz), 8.28 (1H, d, J=7Hz)

Example 17

8-(2-Chloro-6-methylbenzoylamino)-3-(1-hydroxy-1-methylethyl)-2-methylimidazo[1,2-a]pyridine

mp : 220-222°C

NMR ($CDCl_3$:CD_3OD = 20:1, δ) : 1.76 (6H, s), 2.42 (3H, s), 2.47 (3H, s), 6.81 (1H, t, J=8Hz), 7.17 (1H, m), 7.25-7.30 (3H, m), 8.37 (1H, d, J=8Hz), 8.58 (1H, d, J=8Hz)

Example 18

8-(2,6-Dichlorobenzoylamino)-2-(2,2-dimethylpropyl)-imidazo[1,2-a]pyridine

mp : 201-202°C

NMR ($CDCl_3$, δ) : 0.98 (9H, s), 2.62 (2H, s), 6.80 (1H, t, J=7Hz), 7.30-7.45 (4H, m), 7.85 (1H, d, J=7Hz), 8.31 (1H, d, J=7Hz)

Example 19

8-(2-Chlorobenzoylamino)-2-methylimidazo[1,2-a]pyridine

mp : 110°C

NMR ($CDCl_3$, δ) : 2.43 (3H, s), 6.79 (1H, t, J=7.5Hz), 7.33-7.52 (4H, m), 7.72 (1H, dd, J=1.5Hz and 7.5Hz), 7.83 (1H, dd, J=1.5Hz and 7.5Hz), 8.29 (1H, dd, J=1.5Hz and 7.5Hz), 9.07 (1H, br s)

Example 20

8-Benzoylamino-2-methylimidazo[1,2-a]pyridine

mp : 114-115°C

NMR ($CDCl_3$, δ) : 2.46 (3H, s), 6.78 (1H, t, J=7.5Hz), 7.35 (1H, s), 7.47-7.62 (3H, m), 7.80 (1H, dd, J=1.5Hz and 7.5Hz), 8.02 (2H, dd, J=1.5Hz and 7.5Hz), 8.27 (1H, dd, J=1.5Hz and 7.5Hz), 9.22 (1H, br s)

Example 21

2-Methyl-8-(2-methylbenzoylamino)imidazo[1,2-a]pyridine

mp : 124-128°C

NMR ($CDCl_3$, δ) : 2.43 (3H, s), 2.55 (3H, s), 6.79 (1H, t, J=7.5Hz), 7.24-7.43 (4H, m), 7.61 (1H, d, J=7.5Hz), 7.82 (1H, dd, J=1.5Hz and 7.5Hz), 8.29 (1H, dd, J=1.5Hz and 7.5Hz), 8.85 (1H, br s)

Example 22

8-(Biphenyl-2-yl)carbonylamino-2-methylimidazo[1,2-a]-pyridine

NMR ($CDCl_3$, δ) : 2.35 (3H, s), 6.68 (1H, t, J=7.5Hz), 7.20-7.57 (9H, m), 7.69-7.78 (2H, m), 8.09 (1H, d, J=7.5Hz), 8.51 (1H, br s)

Example 23

8-(2-Methoxybenzoylamino)-2-methylimidazo[1,2-a]pyridine

mp : 123-124°C

Example 24

8-(2,6-Dimethylbenzoylamino)-2-methylimidazo-[1,2-a]pyridine

mp : 95-102°C

Example 25

8-(2,6-Difluorobenzoylamino)-2-methylimidazo-[1,2-a]pyridine

mp : 183-185°C

NMR ($CDCl_3$, δ) : 2.42 (3H, s), 6.78 (1H, t, J=7.5Hz), 6.96-7.08 (2H, m), 7.35 (1H, s), 7.45 (1H, m), 7.81 (1H, dd, J=7.5Hz and 1.5Hz), 8.28 (1H, dd, J=7.5Hz and 1.5Hz), 8.99 (1H, br s)

Example 26

8-(2,6-Dichloro-3-methoxybenzoylamino)-2-methylimidazo[1,2-a]pyridine

mp : 210-211°C

Example 27

8-(2,6-Dichloro-3-nitrobenzoylamino)-2-methylimidazo[1,2-a]pyridine

mp : 227-231°C

Example 28

8-(2,4-Dichlorobenzoylamino)-2-trifluoromethylimidazo-[1,2-a]pyridine

mp : 139-140°C

NMR ($CDCl_3$, δ) : 6.98 (1H, t, J=7.5Hz), 7.41 (1H, dd, J=7.5Hz and 1.5Hz), 7.54 (1H, d, J=2Hz), 7.70 (1H, d, J=7.5Hz), 7.93 (1H, dd, J=7.5Hz and 2Hz), 8.41 (1H, d, J=7.5Hz), 9.17 (1H, br s)

Example 29

8-(2,6-Dichlorobenzoylamino)-2-ethylimidazo[1,2-a]-

pyridine

mp : 174-176°C

NMR ($CDCl_3$, δ) : 1.32 (3H, t, J=7.5Hz), 2.79 (2H, q, J=7.5Hz), 6.80 (1H, t, J=7.5Hz), 7.31-7.42 (4H, m), 7.85 (1H, dd, J=7.5Hz and 1.0Hz), 8.32 (1H, dd, J=7.5Hz and 1.0Hz), 8.72 (1H, br s)

Example 30

8-(2,6-Dichlorobenzoylamino)imidazo[1,2-a]pyridine

mp : 163-164°C

NMR ($CDCl_3$, δ) : 6.87 (1H, t, J=7Hz), 7.30-7.40 (3H, m), 7.50 (1H, s), 7.60 (1H, s), 7.92 (1H, d, J=7Hz), 8.35 (1H, d, J=7Hz), 8.92 (1H, br s)

Example 31

8-(2,6-Dichlorobenzoylamino)-2-phenylimidazo[1,2-a]-pyridine

mp : 224-226°C

NMR ($CDCl_3$, δ) : 6.85 (1H, t, J=7Hz), 7.25-7.50 (6H, m), 7.83 (1H, s), 7.85-7.95 (3H, m), 8.37 (1H, d, J=7Hz), 9.00 (1H, br s)

Example 32

8-(2,6-Dichlorobenzoylamino)-2-methyl-3-benzylimidazo-[1,2-a]pyridine

mp : 100-106°C

NMR ($CDCl_3$, δ) : 2.47 (3H, s), 4.25 (2H, s), 6.72 (1H, t, J=7Hz), 7.05-7.15 (2H, m), 7.20-7.40 (6H, m), 7.48 (1H, d, J=7Hz), 8.32 (1H, d, J=7Hz)

Example 33

8-(2,6-Dichlorobenzoylamino)-2,3-dimethylimidazo-[1,2-a]pyridine

mp : 224-226°C

NMR ($CDCl_3$, δ) : 2.49 (3H, s), 2.51 (3H, s), 6.87 (1H,

t, J=7Hz), 7.25-7.40 (3H, m), 7.60 (1H, d, J=7Hz), 8.32 (1H, d, J=7Hz)

Example 34

8-(2,6-Dichlorobenzoylamino)-3-ethoxycarbonyl-2-methylimidazo[1,2-a]pyridine

mp : 145-149°C

NMR ($CDCl_3$, δ) : 1.48 (3H, t, J=7.5Hz), 2.71 (3H, s), 4.47 (2H, q, J=7.5Hz), 7.06 (1H, t, J=7.5Hz), 7.35-7.44 (3H, m), 8.58 (1H, dd, J=7.5Hz and 1.0Hz), 8.80 (1H, br s), 9.06 (1H, dd, J=7.5Hz and 1.0Hz)

Example 35

8-(2,6-Dichlorobenzoylamino)-2-ethoxycarbonylimidazo-[1,2-a]pyridine

mp : 213-215°C

NMR ($CDCl_3$, δ) : 1.41 (3H, t, J=7.5Hz), 4.45 (2H, q, J=7.5Hz), 6.95 (1H, t, J=7.5Hz), 7.33-7.45 (3H, m), 7.91 (1H, dd, J=7.5Hz and 1.5Hz), 8.19 (1H, s), 8.49 (1H, dd, J=7.5Hz and 1.5Hz), 8.91 (1H, br s)

Example 36

8-(2-Chloro-6-methylbenzoylamino)-2-trifluoromethylimidazo[1,2-a]pyridine

NMR ($CDCl_3$, δ) : 2.42 (3H, s), 6.98 (1H, t, J=7Hz), 7.18 (1H, m), 7.25-7.35 (2H, m), 7.91 (1H, s), 7.93 (1H, d, J=7Hz), 8.51 (1H, d, J=7Hz), 8.67 (1H, br s)

Example 37

8-(2,6-Dichlorobenzoylamino)-3-ethoxycarbonyl-2-trifluoromethylimidazo[1,2-a]pyridine

mp : 206-207°C

NMR ($CDCl_3$, δ) : 1.45 (3H, t, J=7Hz), 4.48 (2H, q, J=7Hz), 7.22 (1H, t, J=7Hz), 7.30-7.45 (3H, m),

8.70 (1H, d, J=7Hz), 8.79 (1H, br s), 9.13 (1H, d, J=7Hz)

Example 38

2-Methyl-8-(2,4,6-tribromobenzoylamino)imidazo-[1,2-a]pyridine

mp : 200-201.5°C

NMR ($CDCl_3$, δ) : 2.43 (3H, s), 6.80 (1H, t, J=8Hz), 7.37 (1H, s), 7.78 (2H, s), 7.83 (1H, d, J=8Hz), 8.29 (1H, d, J=8Hz), 8.70 (1H, br s)

Example 39

8-(2,5-Dichlorobenzoylamino)-2-methylimidazo-[1,2-a]pyridine

mp : ~140°C (dec.)

NMR ($CDCl_3$, δ) : 2.43 (3H, s), 6.80 (1H, t, J=8Hz), 7.35 (1H, s), 7.40 (2H, s), 7.70 (1H, s), 7.82 (1H, d, J=8Hz), 8.24 (1H, d, J=8Hz), 9.10 (1H, br s)

Example 40

8-[3,5-Bis(1,1-dimethylethyl)benzoylamino]-2-methylimidazo[1,2-a]pyridine

mp : 104-107°C

NMR ($CDCl_3$, δ) : 1.40 (18H, s), 2.47 (3H, s), 6.79 (1H, t, J=8Hz), 7.36 (1H, s), 7.64 (1H, t, J=2Hz), 7.78-7.82 (3H, m), 8.24 (1H, d, J=8Hz), 9.20 (1H, br s)

Example 41

8-(3-Butoxy-2,6-dichlorobenzoylamino)-2-methylimidazo[1,2-a]pyridine

mp : 73-83°C

NMR ($CDCl_3$, δ) : 1.00 (3H, t, J=6Hz), 1.42-1.60 (2H, m), 1.83 (2H, quint., J=6Hz), 2.42 (3H, s), 4.08 (2H, t, J=6Hz), 6.79 (1H, t, J=8Hz), 6.93 (1H, d,

J=8Hz), 7.30 (1H, d, J=8Hz), 7.35 (1H, s), 7.82 (1H, d, J=8Hz), 8.33 (1H, d, J=8Hz), 8.68 (1H, br s)

Example 42

8-(2,6-Dimethoxybenzoylamino)-2-methylimidazo-[1,2-a]pyridine

mp : 154-156°C (dec.)

NMR ($CDCl_3$, δ) : 2.41 (3H, s), 3.81 (6H, s), 6.59 (2H, d, J=8Hz), 6.77 (1H, t, J=8Hz), 7.27-7.38 (2H, m), 7.78 (1H, d, J=8Hz), 8.39 (1H, d, J=8Hz), 8.73 (1H, br s)

Example 43

8-(2,6-Dichloro-3-nitrobenzoylamino)-3-(1-hydroxy-1-methylethyl)-2-methylimidazo[1,2-a]pyridine

mp : 229-230°C

NMR (DMSO-d_6, δ) : 1.65 (6H, s), 2.47 (3H, s), 5.46 (1H, s), 6.87 (1H, t, J=8Hz), 7.83 (1H, d, J=8Hz), 8.06 (1H, d, J=8Hz), 8.18 (1H, d, J=8Hz), 8.63 (1H, d, J=8Hz)

Example 44

3-Acetyl-8-(2,6-dichlorobenzoylamino)-2-methylimidazo[1,2-a]pyridine

mp : 236-238°C

NMR ($CDCl_3$, δ) : 2.62 (3H, s), 2.77 (3H, s), 7.08 (1H, t, J=8Hz), 7.30-7.43 (3H, m), 8.63 (1H, d, J=8Hz), 8.87 (1H, br s), 9.45 (H, d, J=8Hz)

Example 45

8-(2,6-Dichlorobenzoylamino)-3-methoxy-2-methylimidazo[1,2-a]pyridine

mp : 238-240°C

NMR ($CDCl_3$, δ) : 2.40 (3H, s), 3.98 (3H, s), 6.82 (1H,

t, J=8Hz), 7.28-7.40 (3H, m), 7.69 (1H, d, J=8Hz), 8.27 (1H, d, J=8Hz), 8.67 (1H, m)

Example 46

2-Methyl-8-(1-naphthoylamino)imidazo[1,2-a]pyridine

mp : 167-169°C

NMR ($CDCl_3$, δ) : 2.41 (3H, s), 6.85 (1H, t, J=8Hz), 7.35 (1H, s), 7.50-7.62 (3H, m), 7.80-8.05 (4H, m), 8.38-8.47 (2H, m), 9.15 (1H, br s)

Example 47

8-(2,6-Dichlorobenzoylamino)-2-ethoxycarbonyl-3-methylimidazo[1,2-a]pyridine

mp : 254-256°C

NMR ($CDCl_3$, δ) : 1.43 (3H, t, J=7Hz), 2.80 (3H, s), 4.47 (2H, q, J=7Hz), 6.98 (1H, t, J=8Hz), 7.31-7.42 (3H, m), 7.71 (1H, d, J=8Hz), 8.49 (1H, d, J=8Hz), 8.95 (1H, br s)

Example 48

8-(2,6-Dichlorocinnamoylamino)-2-methylimidazo-[1,2-a]pyridine

mp : ~210°C (dec.)

NMR ($CDCl_3$, δ) : 2.47 (3H, s), 6.79 (1H, t, J=8Hz), 6.95 (1H, d, J=15Hz), 7.20 (1H, m), 7.32-7.42 (3H, m), 7.80 (1H, d, J=8Hz), 7.93 (1H, d, J=15Hz), 8.30 (1H, d, J=8Hz), 8.88 (1H, br s)

Example 49

3-Bromo-8-[N-(2,6-dichlorophenyl)carbamoyl]-2-methylimidazo[1,2-a]pyridine

mp : 237-239°C

NMR ($CDCl_3$, δ) : 2.50 (3H, s), 7.10 (1H, t, J=7Hz), 7.16-7.28 (1H, m), 7.45 (2H, d, J=9Hz), 8.24 (1H, d, J=7Hz), 8.32 (1H, d, J=7Hz)

Example 50

2-Methyl-8-phenylglyoxyloylaminoimidazo[1,2-a]pyridine

mp : 149.5-150.0°C

NMR ($CDCl_3$, δ) : 2.49 (3H, s), 6.79 (1H, t, J=7Hz), 7.36 (1H, s), 7.45-7.60 (2H, m), 7.67 (1H, t, J=7Hz), 7.84 (1H, d, J=7Hz), 8.18 (1H, d, J=7Hz), 8.40 (2H, d, J=7Hz)

Example 51

8-(2,6-Dichlorophenylacetylamino)-2-methylimidazo-[1,2-a]pyridine

mp : 180°C

NMR ($CDCl_3$, δ) : 2.45 (3H, s), 4.26 (2H, s), 6.70 (1H, t, J=7.5Hz), 7.21 (1H, t, J=7.5Hz), 7.33 (1H, s), 7.37 (2H, d, J=7.5Hz), 7.75 (1H, dd, J=7.5Hz and 1.5Hz), 8.07 (1H, dd, J=7.5Hz and 1.5Hz), 8.75 (1H, br s)

Example 52

A mixture of 8-amino-2-methylimidazo[1,2-a]pyridine hydrochloride (734 mg), 2,5-dichlorobenzenesulfonyl chloride (1.23 g) and triethylamine (1.01 g) in dichloromethane (14 ml) was stirred at ambient temperature overnight. The mixture was washed with water and aqueous saturated sodium bicarbonate, dried over sodium sulfate and evaporated in vacuo. The crystalline residue was recrystallized from ethanol to give 8-(2,5-dichlorobenzenesulfonylamino)-2-methylimidazo[1,2-a]pyridine (210 mg).

mp : 210-214°C

NMR ($CDCl_3$, δ) : 2.42 (3H, s), 6.63 (1H, t, J=7.5Hz), 7.09 (1H, dd, J=7.5Hz and 1.5Hz), 7.29 (1H, s), 7.33-7.44 (2H, m), 7.70 (1H, dd, J=7.5Hz and 1.5Hz), 8.17 (1H, d, J=1.5Hz)

Example 53

A mixture of 8-amino-2-methylimidazo[1,2-a]pyridine hydrochloride (367 mg), 1,1'-carbonyldiimidazole (357 mg) and triethylamine (303 mg) in 1,4-dioxane (7 ml) was stirred at ambient temperature for 14 hours. 1,1'-Carbonyldiimidazole (49 mg) was added to the mixture and after 1 hour, 2,6-dimethylpiperidine (283 mg) was added. The mixture was stirred at 60°C for 3 hours and diluted with a mixture of dichloromethane and ethanol (8:2). The solution was washed with brine, dried over sodium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel to give 8-(2,6-dimethylpiperidin-1-yl)carbonylamino-2-methylimidazo[1,2-a]pyridine (176 mg).

oil

NMR ($CDCl_3$, δ) : 1.38 (6H, d, J=7Hz), 1.49-1.88 (6H, m), 2.43 (3H, s), 4.39-4.54 (2H, m), 6.70 (1H, t, J=8Hz), 7.30 (1H, s), 7.66 (1H, d, J=8Hz), 7.91 (1H, d, J=8Hz), 8.00 (1H, br s)

Example 54

A mixture of 8-amino-2-trifluoromethylimidazo-[1,2-a]pyridine (1.0 g) and 2,6-dichlorophenyl isocyanate (940 mg) in dichloromethane (20 ml) was stirred at ambient temperature overnight. The separated solid was collected and washed with dichloromethane and hexane to give 8-[3-(2,6-dichlorophenyl)ureido]-2-trifluoromethylimidazo[1,2-a]-pyridine (1.32 g). The second crop was obtained from the mother liquid (0.43 g).

mp : 204-205°C

NMR (DMSO-d_6, δ) : 7.02 (1H, t, J=7.5Hz), 7.36 (1H, t, J=7.5Hz), 7.58 (2H, d, J=7.5Hz), 7.99 (1H, d, J=7.5Hz), 8.23 (1H, d, J=7.5Hz), 8.60 (1H, s), 9.29 (1H, s), 9.49 (1H, s)

The following compound was obtained according to a

similar manner to that of Example 2.

Example 55

8-(2,6-Dichlorobenzoylamino)-2-methylimidazo-[1,2-a]pyrazine

NMR ($CDCl_3$, δ) : 2.30 (3H, s), 6.74 (1H, d, J=6Hz), 6.90 (1H, s), 7.23-7.35 (3H, m), 7.62 (1H, d, J=6Hz), 8.83 (1H, s)

ESI-MASS (M^++1) : 321

Example 56

A mixture of 8-(2,6-dichlorobenzoylamino)-2-methylimidazo[1,2-a]pyridine (296 mg), 4-pyridinecarbaldehyde (856 mg) and conc. hydrochloric acid (1.6 ml) in acetic acid (8 ml) was stirred at 100°C for 1 day. The reaction mixture was cooled and evaporated in vacuo. To the residue was added aqueous saturated sodium bicarbonate and the separated oil was extracted with ethyl acetate. The extract was washed with brine, dried over sodium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel. The less polar fractions were combined and evaporated in vacuo. The residue was crystallized from diethyl ether to give 8-(2,6-dichlorobenzoylamino)-2-methyl-3-(pyridin-4-yl)carbonylimidazo[1,2-a]pyridine (230 mg).

mp : 234-236°C

NMR (DMSO-d_6, δ) : 2.40 (3H, s), 7.32 (1H, t, J=7Hz), 7.45-7.55 (3H, m), 7.64 (2H, d, J=6Hz), 8.47 (1H, d, J=7Hz), 8.80 (2H, d, J=6Hz), 9.28 (1H, d, J=7Hz)

The more polar fractions were combined and evaporated in vacuo. The residue was dissolved in methanolic hydrogen chloride and the solution was evaporated in vacuo. The residue was crystallized from diethyl ether to give 8-(2,6-dichlorobenzoylamino)-3-hydroxy(pyridin-4-yl)methyl-2-methylimidazo[1,2-a]pyridine dihydrochloride (80 mg).

mp : 209-212°C

NMR (DMSO-d_6, δ) : 6.68 (1H, s), 7.33 (1H, t, J=7Hz), 7.50-7.60 (3H, m), 8.02 (2H, d, J=6Hz), 8.27 (1H, d, J=7Hz), 8.60 (1H, d, J=7Hz), 8.85 (2H, d, J=6Hz), 11.65 (1H, s)

The following compound was obtained according to a similar manner to that of Example 56.

Example 57

8-(2,6-Dichlorobenzoylamino)-3-hydroxy(pyridin-4-yl)methyl-2-trifluoromethylimidazo[1,2-a]pyridine dihydrochloride

mp : ~230°C

NMR (DMSO-d_6, δ) : 6.66 (1H, s), 7.07 (1H, t, J=7Hz), 7.45-7.60 (3H, m), 7.85 (2H, d, J=6Hz), 8.12 (1H, d, J=7Hz), 8.27 (1H, d, J=7Hz), 8.79 (2H, d, J=6Hz)

Example 58

A mixture of 8-(2,6-dichlorobenzoylamino)-2-methylimidazo[1,2-a]pyridine (1.5 g), 37% formalin (5 ml) and conc. hydrochloric acid (2.7 ml) in acetic acid (22 ml) was stirred at 85°C for 5 hours. The mixture was evaporated in vacuo and toluene (20 ml) was added to the mixture. The mixture was evaporated in vacuo and to the mixture was added aqueous saturated sodium bicarbonate. The separated oil was extracted with a mixture of dichloromethane and ethanol (8:2). The extract was washed with brine, dried over sodium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel. The obtained oil was crystallized from ethyl acetate and recrystallized from ethanol to give 8-(2,6-dichlorobenzoylamino)-3-hydroxymethyl-2-methylimidazo[1,2-a]pyridine (1.27 g).

mp : >250°C

NMR ($CDCl_3$:CD_3OD = 9:1, δ) : 2.40 (3H, s), 4.88 (2H, s), 6.93 (1H, t, J=7Hz), 7.30-7.45 (3H, m), 8.03 (1H, d, J=7Hz), 8.42 (1H, d, J=7Hz)

The following compounds (Examples 59 to 60) were obtained according to a similar manner to that of Example 58.

Example 59

8-(2-Chloro-6-methylbenzoylamino)-3-hydroxymethyl-2-trifluoromethylimidazo[1,2-a]pyridine

mp : 204-206°C

NMR ($CDCl_3$, δ) : 2.29 (1H, t, J=7Hz), 2.40 (3H, s), 5.09 (2H, d, J=7Hz), 7.04 (1H, t, J=7Hz), 7.15 (1H, m), 7.20-7.30 (2H, m), 8.08 (1H, d, J=7Hz), 8.57 (1H, d, J=7Hz), 8.78 (1H, br s)

Example 60

8-(2,6-Dichlorobenzoylamino)-3-N,N-dimethylaminomethylimidazo[1,2-a]pyridine

NMR ($CDCl_3$, δ) : 2.25 (6H, s), 3.70 (2H, s), 6.90 (1H, t, J=8Hz), 7.29-7.40 (4H, m), 8.10 (1H, d, J=8Hz), 8.38 (1H, d, J=8Hz), 8.87 (1H, m)

Example 61

A mixture of 8-(2,6-dichlorobenzoylamino)-2-(1,1-dimethylethyl)imidazo[1,2-a]pyridine (181 mg) and N-bromosuccinimide (89 mg) in a mixture of ethanol (2 ml) and tetrahydrofuran (2 ml) was stirred at ambient temperature for 1 hour. The reaction mixture was partitioned between dichloromethane and aqueous saturated sodium bicarbonate. The organic layer was separated, dried over sodium sulfate and evaporated in vacuo. The obtained oil was crystallized from a mixture of diethyl ether and hexane to give 3-bromo-8-(2,6-dichlorobenzoylamino)-2-(1,1-dimethylethyl)imidazo-[1,2-a]pyridine (190 mg).

mp : 163-165°C

NMR ($CDCl_3$, δ) : 1.49 (9H, m), 6.98 (1H, t, J=7Hz), 7.30-7.45 (3H, m), 7.90 (1H, d, J=7Hz), 8.35 (1H, d, J=7Hz), 8.77 (1H, br s)

The following compounds (Examples 62 to 93) were obtained according to a similar manner to that of Example 61.

Example 62

3-Bromo-8-(2,6-dichlorobenzoylamino)-2-(2,2-dimethylpropyl)imidazo[1,2-a]pyridine

mp : 146-149°C

NMR ($CDCl_3$, δ) : 1.00 (9H, s), 2.65 (2H, s), 6.97 (1H, t, J=7Hz), 7.30-7.45 (3H, m), 7.88 (1H, d, J=7Hz), 8.40 (1H, d, J=7Hz), 8.79 (1H, br s)

Example 63

3-Bromo-8-(2,6-dichlorobenzoylamino)-2-methylimidazo[1,2-a]pyridine

mp : 236-239°C

NMR (DMSO-d_6, δ) : 2.38 (3H, s), 7.08 (1H, t, J=7.5Hz), 7.43-7.58 (3H, m), 8.08 (1H, d, J=7.5Hz), 8.18 (1H, d, J=7.5Hz)

Example 64

3-Bromo-8-(2-chlorobenzoylamino)-2-methylimidazo-[1,2-a]pyridine

mp : 166-169°C

NMR (DMSO-d_6, δ) : 2.37 (3H, s), 7.08 (1H, t, J=7.5Hz), 7.40-7.66 (4H, m), 8.08 (2H, d, J=7.5Hz)

Example 65

8-Benzoylamino-3-bromo-2-methylimidazo[1,2-a]pyridine

mp : 147-148°C

NMR (DMSO-d_6, δ) : 2.39 (3H, s), 7.08 (1H, t,

J=7.5Hz), 7.53-7.70 (3H, m), 7.95-8.14 (4H, m), 9.97 (1H, br s)

Example 66

3-Bromo-2-methyl-8-(2-methylbenzoylamino)imidazo-[1,2-a]pyridine

mp : 146-150°C

NMR ($CDCl_3$, δ) : 2.41 (3H, s), 2.53 (3H, s), 6.94 (1H, t, J=7.5Hz), 7.25-7.45 (3H, m), 7.60 (1H, dd, J=1.5Hz and 7.5Hz), 7.81 (1H, dd, J=1.5Hz and 7.5Hz), 8.35 (1H, dd, J=1.5Hz and 7.5Hz), 8.79 (1H, br s)

Example 67

8-(Biphenyl-2-yl)carbonylamino-3-bromo-2-methylimidazo[1,2-a]pyridine

mp : 138-140°C

NMR ($CDCl_3$, δ) : 2.36 (3H, s), 6.85 (1H, t, J=7.5Hz), 7.21-7.60 (8H, m), 7.70-7.81 (2H, m), 8.20 (1H, d, J=7.5Hz), 8.47 (1H, br s)

Example 68

3-Bromo-8-(2-methoxybenzoylamino)-2-methylimidazo-[1,2-a]pyridine

mp : 158-160°C

NMR ($CDCl_3$, δ) : 2.49 (3H, s), 4.21 (3H, s), 6.90 (1H, t, J=7.5Hz), 7.06-7.20 (2H, m), 7.54 (1H, td, J=7.5Hz and 1.5Hz), 7.79 (1H, dd, J=1.5Hz and 7.5Hz), 8.29-8.40 (2H, m)

Example 69

3-Bromo-8-(2,6-dimethylbenzoylamino)-2-methylimidazo[1,2-a]pyridine

mp : 120-123°C

NMR ($CDCl_3$, δ) : 2.38 (6H, s), 2.42 (3H, s), 6.96 (1H,

t, J=7.5Hz), 7.07 (2H, d, J=7.5Hz), 7.21 (1H, d, J=7.5Hz), 7.83 (1H, dd, J=7.5Hz and 1.5Hz), 8.43 (1H, dd, J=7.5Hz and 1.5Hz), 8.60 (1H, br s)

Example 70

3-Bromo-8-(2,6-difluorobenzoylamino)-2-methylimidazo[1,2-a]pyridine

mp : 224-227°C

NMR ($CDCl_3$, δ) : 2.43 (3H, s), 6.91-7.06 (3H, m), 7.44 (1H, m), 7.82 (1H, dd, J=7.5Hz and 1.5Hz), 8.38 (1H, dd, J=7.5Hz and 1.5Hz), 9.05 (1H, br s)

Example 71

3-Bromo-8-(2,6-dichloro-3-methoxybenzoylamino)-2-methylimidazo[1,2-a]pyridine

mp : 229-230°C

NMR (DMSO-d_6, δ) : 2.37 (3H, s), 3.91 (3H, s), 7.08 (1H, t, J=7.5Hz), 7.25 (1H, d, J=7.5Hz), 7.48 (1H, d, J=7.5Hz), 8.08 (1H, d, J=7.5Hz), 8.17 (1H, d, J=7.5Hz)

Example 72

3-Bromo-8-(2,6-dichloro-3-nitrobenzoylamino)-2-methylimidazo[1,2-a]pyridine

mp : 247-248°C (dec.)

NMR ($CDCl_3$:CD_3OD = 20:1, δ) : 2.40 (3H, s), 7.03 (1H, t, J=7.5Hz), 7.61 (1H, d, J=7.5Hz), 7.92 (1H, dd, J=7.5Hz and 1.5Hz), 7.98 (1H, d, J=7.5Hz), 8.44 (1H, dd, J=7.5Hz and 1.5Hz)

Example 73

3-Bromo-8-(2,6-dichlorobenzoylamino)-2-trifluoromethylimidazo[1,2-a]pyridine

mp : 186-188°C

NMR ($CDCl_3$, δ) : 7.13 (1H, t, J=7.5Hz), 7.33-7.45 (3H,

m), 7.99 (1H, dd, J=7.5Hz and 1.5Hz), 8.58 (1H, dd, J=7.5Hz and 1.5Hz), 8.72 (1H, br s)

Example 74

3-Bromo-8-(2,4-dichlorobenzoylamino)-2-trifluoromethylimidazo[1,2-a]pyridine

mp : 162-164°C

NMR ($CDCl_3$, δ) : 7.11 (1H, t, J=7.5Hz), 7.40 (1H, dd, J=7.5Hz and 1.5Hz), 7.52 (1H, d, J=1.5Hz), 7.75 (1H, d, J=7.5Hz), 7.97 (1H, dd, J=7.5Hz and 1.5Hz), 8.49 (1H, d, J=7.5Hz), 9.21 (1H, br s)

Example 75

3-Bromo-8-(2,6-dichlorobenzoylamino)-2-ethylimidazo-[1,2-a]pyridine

mp : 226-228°C

NMR ($CDCl_3$, δ) : 1.29 (3H, t, J=7.5Hz), 2.77 (2H, q, J=7.5Hz), 6.96 (1H, t, J=7.5Hz), 7.29-7.41 (3H, m), 7.85 (1H, dd, J=7.5Hz and 1.5Hz), 8.41 (1H, dd, J=7.5Hz and 1.5Hz), 8.79 (1H, br s)

Example 76

3-Bromo-8-(2,6-dichlorobenzoylamino)imidazo-[1,2-a]pyridine

mp : 200-203°C

NMR ($CDCl_3$, δ) : 7.40 (1H, t, J=7Hz), 7.25-7.35 (3H, m), 7.47 (1H, s), 7.91 (1H, d, J=7Hz), 8.45 (1H, d, J=7Hz), 9.10 (1H, br s)

Example 77

3-Bromo-8-(2,6-dichlorobenzoylamino)-2-phenylimidazo[1,2-a]pyridine

mp : 210-211°C

NMR ($CDCl_3$, δ) : 7.02 (1H, t, J=7Hz), 7.30-7.50 (6H, m), 7.96 (1H, d, J=7Hz), 8.07 (2H, d, J=7Hz), 8.48

(1H, d, J=7Hz), 9.10 (1H, br s)

Example 78

3-Bromo-8-(2,6-dichlorobenzoylamino)-2-ethoxycarbonylimidazo[1,2-a]pyridine

mp : 249-250°C

NMR ($CDCl_3$, δ) : 1.45 (3H, t, J=7.5Hz), 4.50 (2H, q, J=7.5Hz), 7.11 (1H, t, J=7.5Hz), 7.33-7.45 (3H, m), 8.00 (1H, d, J=7.5Hz), 8.58 (1H, dd, J=7.5Hz and 1.5Hz), 8.90 (1H, br s)

Example 79

3-Bromo-2-methyl-8-phenylglyoxyloylaminoimidazo-[1,2-a]pyridine

mp : 162-163°C

NMR ($CDCl_3$, δ) : 2.49 (3H, s), 6.93 (1H, t, J=7Hz), 7.53 (2H, t, J=7Hz), 7.68 (1H, t, J=7Hz), 7.85 (1H, d, J=7Hz), 8.27 (1H, d, J=7Hz), 8.41 (2H, d, J=7Hz), 10.00 (1H, br s)

Example 80

3-Bromo-8-(2,5-dichlorobenzenesulfonylamino)-2-methylimidazo[1,2-a]pyridine

mp : 194-198°C

Example 81

3-Bromo-8-[3-(2,6-dichlorophenyl)ureido]-2-trifluoromethylimidazo[1,2-a]pyridine

mp : 226-228°C

NMR (DMSO-d_6, δ) : 7.19 (1H, t, J=7.5Hz), 7.47 (1H, t, J=7.5Hz), 7.58 (2H, d, J=7.5Hz), 8.06-8.15 (2H, m), 9.31 (1H, s), 9.45 (1H, s)

Example 82

3-Bromo-8-(2,6-dichlorophenylacetylamino)-2-

methylimidazo[1,2-a]pyridine

mp : 185-186°C

NMR ($CDCl_3$, δ) : 2.47 (3H, s), 4.28 (2H, s), 6.86 (1H, t, J=7.5Hz), 7.22 (1H, t, J=7.5Hz), 7.39 (2H, d, J=7.5Hz), 7.78 (1H, dd, J=1.5Hz and 7.5Hz), 8.18 (1H, dd, J=1.5Hz and 7.5Hz), 8.86 (1H, br s)

Example 83

3-Bromo-2-methyl-8-(1-naphthoylamino)imidazo-[1,2-a]pyridine

mp : 179-180°C

NMR ($CDCl_3$, δ) : 2.40 (3H, s), 6.59 (1H, t, J=8Hz), 7.50-7.63 (3H, m), 7.79-7.96 (3H, m), 8.00 (1H, d, J=8Hz), 8.44 (2H, t, J=8Hz), 9.00 (1H, br s)

Example 84

3-Bromo-2-methyl-8-(2,4,6-tribromobenzoylamino)-imidazo[1,2-a]pyridine

mp : 192-195°C

NMR ($CDCl_3$, δ) : 2.45 (3H, s), 6.96 (1H, t, J=8Hz), 7.78 (2H, s), 7.85 (1H, d, J=8Hz), 8.38 (1H, d, J=8Hz), 8.66 (1H, br s)

Example 85

3-Bromo-8-(2,6-dichlorocinnamoylamino)-2-methylimidazo[1,2-a]pyridine

mp : 219-221°C

NMR ($CDCl_3$, δ) : 2.48 (3H, s), 6.91 (1H, d, J=15Hz), 6.94 (1H, t, J=8Hz), 7.20 (1H, m), 7.39 (2H, d, J=8Hz), 7.81 (1H, d, J=8Hz), 7.95 (1H, d, J=15Hz), 8.39 (1H, d, J=8Hz), 8.74 (1H, br s)

Example 86

3-Bromo-8-(2,5-dichlorobenzoylamino)-2-methylimidazo[1,2-a]pyridine

mp : 200-201.5°C

NMR ($CDCl_3$, δ) : 2.43 (3H, s), 6.94 (1H, t, J=8Hz), 7.41 (2H, s), 7.73 (1H, s), 7.83 (1H, d, J=8Hz), 8.32 (1H, d, J=8Hz), 9.08 (1H, br s)

Example 87

8-[3,5-Bis(1,1-dimethylethyl)benzoylamino]-3-bromo-2-methylimidazo[1,2-a]pyridine

mp : 121°C

NMR ($CDCl_3$, δ) : 1.40 (18H, s), 2.47 (3H, s), 6.94 (1H, t, J=8Hz), 7.64 (1H, s), 7.78-7.84 (3H, m), 8.34 (1H, d, J=8Hz), 9.19 (1H, br s)

Example 88

3-Bromo-8-(3-butoxy-2,6-dichlorobenzoylamino)-2-methylimidazo[1,2-a]pyridine

mp : 144-146°C

NMR ($CDCl_3$, δ) : 1.00 (3H, t, J=6Hz), 1.43-1.60 (2H, m), 1.83 (2H, quint., J=6Hz), 2.42 (3H, s), 4.07 (2H, t, J=6Hz), 6.90-7.00 (2H, m), 7.30 (1H, d, J=8Hz), 7.83 (1H, d, J=8Hz), 8.41 (1H, d, J=8Hz), 8.66 (1H, br s)

Example 89

3-Bromo-8-(2,6-dimethoxybenzoylamino)-2-methylimidazo[1,2-a]pyridine

mp : 223°C (dec.)

NMR ($CDCl_3$, δ) : 2.42 (3H, s), 3.82 (6H, s), 6.59 (2H, d, J=8Hz), 6.93 (1H, t, J=8Hz), 7.34 (1H, t, J=8Hz), 7.79 (1H, d, J=8Hz), 8.48 (1H, d, J=8Hz), 8.76 (1H, br s)

Example 90

3-Bromo-8-(2,6-dimethylpiperidin-1-yl)carbonylamino-2-methylimidazo[1,2-a]pyridine

NMR ($CDCl_3$, δ) : 1.37 (6H, d, J=7Hz), 1.50-1.87 (6H, m), 2.43 (3H, s), 4.38-4.53 (2H, m), 6.34 (1H, t, J=8Hz), 7.66 (1H, d, J=8Hz), 7.93 (1H, br s), 8.00 (1H, d, J=8Hz)

Example 91

3-Chloro-8-(2,6-dichlorobenzoylamino)-2-methylimidazo[1,2-a]pyridine

mp : 212-214°C

NMR (DMSO-d_6, δ) : 2.37 (3H, s), 7.08 (1H, t, J=7.5Hz), 7.42-7.55 (3H, m), 8.09 (1H, dd, J=1.5Hz and 7.5Hz), 8.18 (1H, dd, J=1.5Hz and 7.5Hz)

Example 92

3-Chloro-8-(2,6-dichlorobenzoylamino)-2-trifluoromethylimidazo[1,2-a]pyridine

mp : 209-213°C

NMR ($CDCl_3$, δ) : 7.14 (1H, t, J=7.5Hz), 7.33-7.45 (3H, m), 7.94 (1H, dd, J=7.5Hz and 1.5Hz), 8.57 (1H, dd, J=7.5Hz and 1.5Hz), 8.69 (1H, br s)

Example 93

3-Bromo-8-(2,6-dichlorobenzoylamino)-2-methylimidazo[1,2-a]pyrazine

mp : 183-185°C

NMR ($CDCl_3$, δ) : 2.29 (3H, s), 6.80 (1H, d, J=7Hz), 7.23-7.35 (3H, m), 7.70 (1H, d, J=7Hz), 8.80 (1H, s)

Example 94

To a solution of 8-(2,6-dichlorobenzoylamino)-2-methylimidazo[1,2-a]pyridine (300 mg) and pyridine (741 mg) in dichloromethane (3 ml) was added methyl chloroformate (0.36 ml). The solution was stirred at ambient temperature overnight and evaporated in vacuo. The crystalline residue

was triturated with ethanol to give 8-(2,6-dichlorobenzoylamino)-3-(1,4-dihydro-1-methoxycarbonylpyridin-4-yl)-2-methylimidazo[1,2-a]pyridine (427 mg).

mp : 209-211°C (dec.)

NMR ($CDCl_3$, δ) : 2.40 (3H, s), 3.90 (3H, s), 4.73-4.90 (3H, m), 6.80 (1H, t, J=8Hz), 6.92-7.15 (2H, m), 7.30-7.40 (3H, m), 7.90 (1H, d, J=8Hz), 8.36 (1H, d, J=8Hz), 8.75 (1H, m)

Example 95

Fuming nitric acid (6 drops) was added dropwise to a mixture of 8-(2,6-dichlorobenzoylamino)-2-methylimidazo-[1,2-a]pyridine (320 mg) in sulfuric acid (1.5 ml) over the period of 30 minutes with ice cooling. The mixture was poured into cold water and made alkaline with aqueous saturated sodium bicarbonate to give a crude solid. The obtained solid was partitioned between ethyl acetate and aqueous saturated sodium bicarbonate. The separated organic layer was dried over sodium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel and the obtained solid was triturated with diethyl ether to give 8-(2,6-dichlorobenzoylamino)-2-methyl-3-nitroimidazo[1,2-a]pyridine (128 mg).

mp : 261-263°C (dec.)

NMR ($CDCl_3$, δ) : 2.82 (3H, s), 7.21-7.30 (1H, m), 7.33-7.44 (3H, m), 8.73-8.80 (2H, m), 9.15 (1H, d, J=8Hz)

Example 96

A mixture of 3-bromo-8-(2,6-dichlorobenzoylamino-2-trifluoromethylimidazo[1,2-a]pyridine (300 mg), 2-(tributylstannyl)pyridine (341 mg) and tetrakis(triphenylphosphine)palladium (15 mg) in 1,4-dioxane (6 ml) was refluxed for 18 hours. The mixture was evaporated in vacuo and the residue was purified by column

chromatography on silica gel. The obtained oil was crystallized from ethanol and the crystalline was dissolved in methanolic hydrogen chloride. The solution was evaporated in vacuo and the residue was crystallized from ethanol to give 8-(2,6-dichlorcbenzoylamino)-3-(pyridin-2-yl)-2-trifluoromethylimidazo[1,2-a]pyridine hydrochloride (65 mg).

mp : 206-208°C

NMR (DMSO-d_6, δ) : 7.17 (1H, t, J=8Hz), 7.49-7.63 (4H, m), 7.75 (1H, d, J=8Hz), 8.10 (1H, t, J=8Hz), 8.35 (1H, d, J=8Hz), 8.42 (1H, d, J=8Hz), 8.87 (1H, m)

The following compounds (Examples 97 to 99) were obtained according to a similar manner to that of Example 96.

Example 97

8-(2,6-Dichlorobenzoylamino)-3-(pyridin-3-yl)-2-trifluoromethylimidazo[1,2-a]pyridine

mp : 217-219°C

NMR ($CDCl_3$, δ) : 7.00 (1H, t, J=8Hz), 7.35-7.45 (3H, m), 7.53 (1H, m), 7.70 (1H, d, J=8Hz), 7.83 (1H, m), 8.58 (1H, d, J=8Hz), 8.72-8.82 (3H, m)

Example 98

3-(3-Aminophenyl)-8-(2,6-dichlorobenzoylamino)-2-trifluoromethylimidazo[1,2-a]pyridine

mp : 204-206°C

NMR ($CDCl_3$, δ) : 3.86 (2H, br s), 6.75 (1H, m), 6.84 (2H, d, J=8Hz), 6.92 (1H, t, J=8Hz), 7.30-7.43 (4H, m), 7.79 (1H, d, J=8Hz), 8.51 (1H, d, J=8Hz), 8.80 (1H, br s)

Example 99

8-(2,6-Dichlorobenzoylamino)-3-(furan-3-yl)-2-trifluoromethylimidazo[1,2-a]pyridine

mp : 206-207°C

NMR ($CDCl_3$, δ) : 6.63 (1H, s), 6.99 (1H, t, J=8Hz), 7.32-7.43 (3H, m), 7.66 (1H, s), 7.73 (1H, s), 7.84 (1H, d, J=8Hz), 8.52 (1H, d, J=8Hz), 8.74 (1H, br s)

Example 100

A mixture of 8-(2,6-dichlorobenzoylamino)-3-hydroxymethyl-2-trifluoromethylimidazo[1,2-a]pyridine (200 mg), triethylamine (100 mg) and methanesulfonyl chloride (68 mg) in 1,2-dichloroethane (2 ml) was stirred at ambient temperature for 1 hour to give 8-(2,6-dichlorobenzoylamino)-3-methylsulfonyloxymethyl-2-trifluoromethylimidazo[1,2-a]-pyridine as the crude product. To the crude product was added dimethylamine hydrochloride (44 mg) and the mixture was refluxed overnight. The mixture was diluted with dichloromethane, washed with brine, dried over sodium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel and the obtained oil was crystallized from diisopropyl ether to give 8-(2,6-dichlorobenzoylamino)-3-dimethylaminomethyl-2-trifluoromethylimidazo[1,2-a]pyridine (146 mg).

mp : 190-193°C

NMR ($CDCl_3$, δ) : 2.25 (6H, s), 3.84 (2H, s), 6.98 (1H, t, J=8Hz), 7.31-7.43 (3H, m), 8.17 (1H, d, J=8Hz), 8.52 (1H, d, J=8Hz), 8.69 (1H, s)

The following compounds (Examples 101 to 121) were obtained according to a similar manner to that of Example 100.

Example 101

8-(2,6-Dichlorobenzoylamino)-3-(imidazol-1-yl)methyl-2-methylimidazo[1,2-a]pyridine

mp : 244-245°C (dec.)

NMR (DMSO-d_6, δ) : 2.47 (3H, s), 5.73 (2H, s), 6.22

(1H, m), 6.96 (1H, t, J=8Hz), 7.41 (1H, m), 7.46-7.54 (3H, m), 7.85 (1H, m), 8.10 (1H, d, J=8Hz), 8.30 (1H, d, J=8Hz)

Example 102

3-[2-(tert-Butoxycarbonyl)hydrazinomethyl]-8-(2,6-dichlorobenzoylamino)-2-methylimidazo[1,2-a]pyridine

mp : 229-230°C

NMR ($CDCl_3$, δ) : 1.49 (9H, s), 2.38 (3H, s), 4.02 (1H, m), 4.20-4.26 (2H, m), 6.80 (1H, t, J=8Hz), 7.07 (1H, m), 7.31-7.40 (3H, m), 7.95 (1H, d, J=8Hz), 8.19 (1H, m), 9.00 (1H, m)

Example 103

8-(2,6-Dichlorobenzoylamino)-3-(morpholin-4-yl)methyl-2-trifluoromethylimidazo[1,2-a]pyridine

mp : 173-174°C

NMR ($CDCl_3$, δ) : 2.50 (4H, t, J=6Hz), 3.69 (4H, t, J=6Hz), 3.93 (2H, s), 7.01 (1H, t, J=8Hz), 7.32-7.44 (3H, m), 8.18 (1H, d, J=8Hz), 8.55 (1H, d, J=8Hz), 8.74 (1H, s)

Example 104

8-(2,6-Dichlorobenzoylamino)-2-methyl-3-[(4-phenylimidazol-1-yl)methyl]imidazo[1,2-a]pyridine

mp : 246-248°C (dec.)

NMR ($CDCl_3$, δ) : 5.42 (2H, s), 6.87 (1H, t, J=8Hz), 7.08 (1H, s), 7.20-7.28 (1H, m), 7.30-7.41 (4H, m), 7.53 (1H, d, J=8Hz), 7.58 (1H, s), 7.71 (2H, d, J=8Hz), 8.42 (1H d, J=8Hz), 8.70 (1H, m)

and

8-(2,6-Dichlorobenzoylamino)-2-methyl-3-[(5-phenylimidazol-1-yl)methyl]imidazo[1,2-a]pyridine

mp : 146-148°C

NMR ($CDCl_3$, δ) : 5.37 (2H, s), 6.75 (1H, t, J=8Hz), 7.12 (1H, s), 7.16 (1H, d, J=8Hz), 7.30-7.51 (8H, m), 8.37 (1H, d, J=8Hz), 8.64 (1H, m)

Example 105

8-(2,6-Dichlorobenzoylamino)-3-(piperidin-1-yl)methyl-2-trifluoromethylimidazo[1,2-a]pyridine dihydrochloride

mp : 236-243°C

NMR (DMSO-d_6, δ) : 1.30-1.90 (6H, m), 3.00-3.16 (2H, m), 3.46-3.61 (2H, m), 4.81 (2H, s), 7.28 (1H, t, J=8Hz), 7.47-7.59 (3H, m), 8.40 (1H, d, J=8Hz), 8.77 (1H, d, J=8Hz)

Example 106

3-[Bis(2-methoxyethyl)]aminomethyl-8-(2,6-dichlorobenzoylamino)-2-trifluoromethylimidazo[1,2-a]pyridine dihydrochloride (amorphous)

NMR ($CDCl_3$, δ) : 3.20-3.65 (4H, m), 3.40 (6H, s), 3.80-4.08 (4H, m), 4.97 (2H, s), 7.25 (1H, br s), 7.32-7.44 (3H, m), 8.67 (1H, d, J=8Hz), 8.71 (1H, s), 9.09 (1H, br s)

Example 107

8-(2,6-Dichlorobenzoylamino)-3-(pyrrolidin-1-yl)methyl-2-trifluoromethylimidazo[1,2-a]pyridine dihydrochloride

mp : >250°C

NMR (DMSO-d_6, δ) : 1.80-1.95 (2H, m), 1.98-2.15 (2H, m), 3.05-3.25 (2H, m), 3.48-3.72 (2H, m), 4.97 (2H, d, J=7Hz), 7.28 (1H, t, J=8Hz), 7.47-7.58 (3H, m), 8.40 (1H, d, J=8Hz), 8.77 (1H, d, J=8Hz)

Example 108

8-(2,6-Dichlorobenzoylamino)-3-[N-methyl-N-(pyridin-2-yl)aminomethyl]-2-trifluoromethylimidazo[1,2-a]pyridine

dihydrochloride

mp : 155-165°C

NMR (DMSO-d_6, δ) : 2.90 (3H, s), 5.39 (2H, s), 7.03 (1H, t, J=8Hz), 7.20 (1H, t, J=8Hz), 7.39 (1H, m), 7.47-7.58 (3H, m), 8.03 (1H, t, J=8Hz), 8.18 (1H, d, J=6Hz), 8.28 (1H, d, J=8Hz), 8.35 (1H, d, J=8Hz)

Example 109

8-(2,6-Dichlorobenzoylamino)-3-[(4-ethoxycarbonylpiperidin-1-yl)methyl]-2-trifluoromethylimidazo[1,2-a]pyridine hydrochloride

mp : 188°C

ESI-MASS : 543 $(M+H)^+$

Example 110

8-(2,6-Dichlorobenzoylamino)-3-(imidazol-1-yl)methyl-2-trifluoromethylimidazo[1,2-a]pyridine hydrochloride

mp : >250°C

NMR (DMSO-d_6, δ) : 6.03 (2H, s), 7.26 (1H, t, J=8Hz), 7.47-7.59 (3H, m), 7.70 (2H, d, J=7Hz), 8.39 (1H, d, J=8Hz), 8.56 (1H, d, J=8Hz), 9.14 (1H, s)

Example 111

8-(2,6-Dichlorobenzoylamino)-3-(2-methylimidazol-1-yl)methyl-2-trifluoromethylimidazo[1,2-a]pyridine hydrochloride

NMR (DMSO-d_6, δ) : 2.73 (3H, s), 5.90 (2H, s), 7.23 (1H, t, J=8Hz), 7.31 (1H, s), 7.48-7.59 (4H, m), 8.37 (1H, d, J=8Hz), 8.40 (1H, d, J=8Hz)

Example 112

8-(2,6-Dichlorobenzoylamino)-3-(1,2,4-triazol-1-yl)methyl-2-trifluoromethylimidazo[1,2-a]pyridine hydrochloride

mp : 144-148°C

NMR (DMSO-d_6, δ) : 6.00 (2H, s), 7.24 (1H, t, J=8Hz), 7.46-7.57 (3H, m), 7.98 (1H, s), 8.33 (1H, d, J=8Hz), 8.60 (1H, d, J=8Hz), 8.81 (1H, s)

Example 113

8-(2,6-Dichlorobenzoylamino)-3-(pyridin-3-yl)oxymethyl-2-trifluoromethylimidazo[1,2-a]pyridine dihydrochloride

mp : >250°C

NMR (DMSO-d_6, δ) : 6.44 (2H, s), 7.29 (1H, t, J=8Hz), 7.48-7.59 (3H, m), 7.91 (1H, dd, J=8Hz and 2Hz), 8.08 (1H, dd, J=8Hz and 2Hz), 8.38-8.45 (2H, m), 8.53-8.60 (2H, m)

Example 114

8-(2,6-Dichlorobenzoylamino)-3-(N-ethylcarbamoyl)-oxymethyl-2-trifluoromethylimidazo[1,2-a]pyridine

mp : 172-174°C

NMR ($CDCl_3$, δ) : 1.13 (3H, t, J=7Hz), 3.23 (2H, quint., J=7Hz), 4.72 (1H, br), 5.55 (2H, s), 7.07 (1H, t, J=8Hz), 7.30-7.45 (3H, m), 8.19 (1H, d, J=8Hz), 8.57 (1H, d, J=8Hz), 8.76 (1H, br s)

Example 115

8-(2,6-Dichlorobenzoylamino)-3-(N,N-dimethylamino)-methyl-2-trifluoromethylimidazo[1,2-a]pyridine dihydrochloride

mp : >250°C

NMR (DMSO-d_6, δ) : 2.85 (6H, s), 4.85 (2H, s), 7.27 (1H, t, J=8Hz), 7.45-7.58 (3H, m), 8.40 (1H, d, J=8Hz), 8.75 (1H, d, J=8Hz)

Example 116

8-(2,6-Dichlorobenzoylamino)-3-[N-methyl-N-(pyridin-3-yl)methylamino]methyl-2-trifluoromethylimidazo[1,2-a]pyridine dihydrochloride

yl)methylamino]methyl-2-trifluoromethylimidazo[1,2-a]pyridine dihydrochloride

mp : 160-173°C

NMR (CD_3OD, δ) : 2.58 (3H, s), 4.26 (2H, br s), 4.59 (2H, br s), 7.26 (1H, t, J=8Hz), 7.41-7.55 (3H, m), 8.01 (1H, t, J=8Hz), 8.49-8.53 (2H, m), 8.61 (1H, d, J=8Hz), 8.77 (1H, d, J=8Hz), 8.90 (1H, s)

Example 117

3-(N-Cyclohexyl-N-methylamino)methyl-8-(2,6-dichlorobenzoylamino)-2-trifluoromethylimidazo[1,2-a]pyridine hydrochloride

mp : 219-223°C

NMR (DMSO-d_6, δ) : 1.14-1.75 (6H, m), 1.81-1.98 (2H, m), 2.11-2.28 (2H, m), 2.65 (3H, d, J=7Hz), 3.41-3.57 (1H, m), 4.62-4.75 (1H, m), 4.99-5.08 (1H, m), 7.29 (1H, t, J=8Hz), 7.46-7.58 (3H, m), 8.40 (1H, d, J=8Hz), 8.68 (1H, d, J=8Hz)

Example 118

8-(2,6-Dichlorobenzoylamino)-3-[N-methyl-N-[2-(pyridin-2-yl)ethyl]amino]methyl-2-trifluoromethylimidazo[1,2-a]-pyridine dihydrochloride

mp : 150-159°C

NMR (DMSO-d_6, δ) : 2.81 (3H, s), 3.47 (2H, t, J=7Hz), 3.65 (2H, t, J=7Hz), 4.88 (2H, s), 7.25 (1H, t, J=8Hz), 7.48-7.72 (5H, m), 8.12-8.20 (1H, m), 8.39 (1H, d, J=8Hz), 8.61-8.70 (2H, m)

Example 119

8-(2,6-Dichlorobenzoylamino)-3-[N-(2-methoxyethyl)-N-methylamino]methyl-2-trifluoromethylimidazo[1,2-a]pyridine hydrochloride

mp : 75-104°C

NMR (DMSO-d_6, δ) : 2.77 (3H, s), 3.36 (3H, s), 3.40-

(1H, d, J=8Hz), 8.64 (1H, d, J=8Hz)

Example 120

8-(2,6-Dichlorobenzoylamino)-3-(N-ethoxycarbonylmethyl-N-methylamino)methyl-2-trifluoromethylimidazo[1,2-a]pyridine hydrochloride

mp : 135-143°C

NMR (DMSO-d_6, δ) : 1.23 (3H, t, J=7Hz), 2.62 (3H, br s), 4.19 (2H, q, J=7Hz), 4.50-4.77 (2H, br), 4.80-5.20 (2H, br), 7.27 (1H, t, J=8Hz), 7.45-7.58 (3H, m), 8.36 (1H, d, J=8Hz), 8.65 (1H, d, J=8Hz)

Example 121

8-(2,6-Dichlorobenzoylamino)-3-(imidazol-1-yl)methyl-2-trifluoromethylimidazo[1,2-a]pyridine (100 mg)

mp : 240-242°C

NMR ($CDCl_3$, δ) : 5.59 (2H, s), 6.90 (1H, s), 7.04 (1H, t, J=8Hz), 7.10 (1H, s), 7.33-7.44 (3H, m), 7.59-7.64 (2H, m), 8.59 (1H, d, J=8Hz), 8.74 (1H, br s)

The following compound was obtained according to a similar manner to that of Example 6.

Example 122

[8-(2,6-Dichlorobenzoylamino)imidazo[1,2-a]pyridin-3-yl]methyltrimethylammonium iodide

mp : 211°C

NMR (DMSO-d_6, δ) : 3.10 (9H, s), 5.00 (2H, s), 7.16 (1H, t, J=8Hz), 7.45-7.57 (3H, m), 7.90 (1H, s), 8.27 (1H, d, J=8Hz), 8.65 (1H, d, J=8Hz)

ESI-MASS : 318 (M^+-(Me_3N+I))

The following compounds (Examples 123 to 125) were obtained according to a similar manner to that of Example 7.

Example 123

3-Carboxy-8-(2,6-dichlorobenzoylamino)-2-methylimidazo[1,2-a]pyridine

mp : 220-221°C

NMR (DMSO-d_6, δ) : 2.63 (3H, s), 7.18 (1H, t, J=7.5Hz), 7.44-7.59 (3H, m), 8.32 (1H, d, J=7.5Hz), 9.09 (1H, d, J=7.5Hz)

Example 124

2-Carboxy-8-(2,6-dichlorobenzoylamino)-3-methylimidazo[1,2-a]pyridine

mp : >250°C

NMR (DMSO-d_6, δ) : 2.75 (3H, s), 7.05 (1H, t, J=8Hz), 7.44-7.57 (3H, m), 8.18 (2H, dd, J=3Hz and 8Hz)

Example 125

Sodium 3-bromo-8-(2,6-dichlorobenzoylamino)imidazo-[1,2-a]pyridin-2-carboxylate

mp : >250°C

NMR (DMSO-d_6, δ) : 7.11 (1H, t, J=7.5Hz), 7.45-7.60 (3H, m), 8.12-8.23 (2H, m)

Example 126

A mixture of [8-(2,6-dichlorobenzoylamino)-2-methylimidazo[1,2-a]pyridin-3-yl]methyltrimethylammonium iodide (300 mg) and sodium cyanide (30 mg) in N,N-dimethylformamide (1.5 ml) was stirred at 90°C for 20 minutes. The mixture was partitioned between ethyl acetate and water. The organic layer was separated, dried over sodium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel and the obtained solid was triturated with diethyl ether to give 3-cyanomethyl-8-(2,6-dichlorobenzoylamino)-2-methylimidazo-[1,2-a]pyridine (111 mg).

mp : 251-255°C

NMR ($CDCl_3$, δ) : 2.44 (3H, s), 3.98 (2H, s), 7.00 (1H, t, J=8Hz), 7.30-7.41 (3H, m), 7.75 (1H, d, J=8Hz), 8.46 (1H, d, J=8Hz), 8.70 (1H, br s)

Example 127

Sodium hydride (60%, 46 mg) was added to 2,2,2-trifluoroethanol (1.5 mg) at 4°C. The mixture was stirred at ambient temperature for 15 minutes and to the mixture was added [8-(2,6-dichlorobenzoylamino)-2-methylimidazo[1,2-a]-pyridin-3-yl]methyltrimethylammonium iodide (300 mg) at 4°C. Then, the mixture was refluxed for 4 hours, cooled and partitioned between ethyl acetate and aqueous saturated sodium bicarbonate. The organic layer was separated, washed with brine, dried over sodium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel and the obtained oil was crystallized from diethyl ether to give 8-(2,6-dichlorobenzoylamino)-2-methyl-3-(2,2,2-trifluoroethoxy)methylimidazo[1,2-a]pyridine (120 mg).

mp : 176-177°C

NMR ($CDCl_3$, δ) : 2.43 (3H, s), 3.78 (2H, q, J=9Hz), 4.95 (2H, s), 6.90 (1H, t, J=8Hz), 7.30-7.40 (3H, m), 7.89 (1H, d, J=8Hz), 8.43 (1H, d, J=8Hz), 8.69 (1H, br s)

The following compound was obtained according to a similar manner to that of Example 127.

Example 128

3-Cyanomethyl-8-(2,6-dichlorobenzoylamino)imidazo-[1,2-a]pyridine

mp : 216-218°C

NMR ($CDCl_3$, δ) : 4.02 (2H, s), 7.06 (1H, t, J=8Hz), 7.30-7.40 (3H, m), 7.53 (1H, s), 7.79 (1H, d, J=8Hz), 8.48 (1H, d, J=8Hz), 8.90 (1H, br s)

The following compounds (Examples 129 to 133) were obtained according to a similar manner to that of Example 9.

Example 129

8-(2,6-Dichlorobenzoylamino)-3-(1-methylimidazol-2-yl)thiomethyl-2-trifluoromethylimidazo[1,2-a]pyridine

mp : 201-202°C

NMR (DMSO-d_6, δ) : 3.38 (3H, s), 4.63 (2H, s), 6.90 (1H, s), 7.20 (1H, t, J=8Hz), 7.26 (1H, s), 7.45-7.60 (3H, m), 8.29-8.38 (2H, m)

Example 130

8-(2,6-Dichlorobenzoylamino)-3-formyl-2-trifluoromethylimidazo[1,2-a]pyridine

mp : 219-222°C

NMR ($CDCl_3$, δ) : 7.32 (1H, t, J=8Hz), 7.36-7.48 (3H, m), 8.76 (1H, br s), 8.84 (1H, d, J=8Hz), 9.36 (1H, d, J=8Hz), 10.22 (1H, s)

Example 131

8-(2,6-Dichlorobenzoylamino)-3-methoxycarbonyloxymethyl-2-trifluoromethylimidazo[1,2-a]pyridine

mp : 170-175°C

NMR ($CDCl_3$, δ) : 3.83 (3H, s), 5.62 (2H, s), 7.10 (1H, t, J=8Hz), 7.33-7.43 (3H, m), 8.08 (1H, d, J=8Hz), 8.60 (1H, d, J=8Hz), 8.73 (1H, s)

Example 132

8-(2,6-Dichlorobenzoylamino)-3-(3-methylsulfonylamino-phenyl)-2-trifluoromethylimidazo[1,2-a]pyridine

mp : ~153°C

NMR ($CDCl_3$, δ) : 3.09 (3H, s), 6.74 (1H, br s), 6.98 (1H, t, J=8Hz), 7.28-7.44 (6H, m), 7.57 (1H, t, J=8Hz), 7.76 (1H, d, J=8Hz), 8.54 (1H, d, J=8Hz), 8.83 (1H, br s)

Example 133

8-(2,6-Dichlorobenzoylamino)-3-(3-lauroylaminophenyl)-2-trifluoromethylimidazo[1,2-a]pyridine

mp : 155-157°C

NMR ($CDCl_3$, δ) : 0.88 (3H, t, J=7Hz), 1.20-1.42 (16H, m), 1.68-1.80 (2H, m), 2.40 (2H, t, J=7Hz), 6.93 (1H, t, J=8Hz), 7.20 (1H, m), 7.32-7.43 (3H, m), 7.51 (1H, t, J=8Hz), 7.64-7.71 (2H, m), 7.80 (1H, d, J=8Hz), 8.52 (1H, d, J=8Hz), 8.78 (1H, br s)

The following compounds (Examples 134 to 159) were obtained according to a similar manner to that of Example 10.

Example 134

8-(2,6-Dichlorobenzoylamino)-2-methyl-3-[N-(3-trifluoromethylphenyl)carbamoyl]methylimidazo[1,2-a]pyridine hydrochloride

mp : 182-203°C

NMR (DMSO-d_6, δ) : 2.53 (3H, s), 4.35 (2H, s), 7.43 (1H, d, J=8Hz), 7.47-7.66 (5H, m), 7.82 (1H, d, J=8Hz), 8.12 (1H, s), 8.63 (1H, d, J=8Hz), 8.70 (1H d, J=8Hz)

Example 135

8-(2,6-Dichlorobenzoylamino)-2-methyl-3-[N-(pyridin-4-yl)methylcarbamoyl]methylimidazo[1,2-a]pyridine dihydrochloride

mp : 195-205°C

NMR (DMSO-d_6, δ) : 2.50 (3H, s), 4.24 (2H, s), 4.55 (2H, d, J=7Hz), 7.50-7.64 (4H, m), 7.88 (2H, d, J=8Hz), 8.64 (1H, d, J=8Hz), 8.68 (1H, d, J=8Hz), 8.84 (2H, d, J=8Hz), 9.18 (1H, t, J=7Hz)

Example 136

8-(2,6-Dichlorobenzoylamino)-3-[[N-(2-hydroxyethyl)]-

carbamoylmethyl]-2-methylimidazo[1,2-a]pyridine

mp : 214-217°C

NMR ($CDCl_3$, δ) : 2.38 (3H, s), 3.34 (2H, t, J=6Hz), 3.60 (2H, t, J=6Hz), 3.82 (2H, s), 6.92 (1H, t, J=8Hz), 7.30-7.44 (3H, m), 7.82 (1H, d, J=8Hz), 8.43 (1H, d, J=8Hz)

Example 137

8-(2,6-Dichlorobenzoylamino)-2-methyl-3-[[N-(thiazol-2-yl)]carbamoylmethyl]imidazo[1,2-a]pyridine hydrochloride

mp : 201-205°C

NMR (DMSO-d_6, δ) : 2.51 (3H, s), 4.40 (2H, s), 7.25 (1H, d, J=5Hz), 7.50-7.65 (5H, m), 8.65-8.69 (2H, m)

Example 138

8-(2,6-Dichlorobenzoylamino)-2-methyl-3-[4-(pyridin-2-yl)piperazin-1-yl-carbonylmethyl]imidazo[1,2-a]pyridine trihydrochloride

mp : >250°C

NMR (DMSO-d_6, δ) : 2.49 (3H, s), 3.57-4.02 (8H, m), 4.40 (2H, s), 6.94 (1H, t, J=8Hz), 7.31 (1H, br), 7.48-7.65 (4H, m), 7.96 (1H, br), 8.10 (1H, d, J=8Hz), 8.49 (1H, d, J=8Hz), 8.65 (1H, d, J=8Hz)

Example 139

8-(2,6-Dichlorobenzoylamino)-2-methyl-3-[(morpholin-4-yl)carbonylmethyl]imidazo[1,2-a]pyridine hydrochloride

mp : >250°C

NMR (DMSO-d_6, δ) : 2.46 (3H, s), 3.46 (2H, t, J=7Hz), 3.55-3.67 (4H, m), 3.73 (2H, t, J=7Hz), 4.31 (2H, s), 7.48 (1H, t, J=8Hz), 7.54-7.66 (3H, m), 8.44 (1H, d, J=8Hz), 8.60 (1H, d, J=8Hz)

Example 140

8-(2,6-Dichlorobenzoylamino)-3-[(4-hydroxypiperidin-1-

yl)carbonylmethyl]-2-methylimidazo[1,2-a]pyridine hydrochloride

mp : >250°C

NMR (DMSO-d_6, δ) : 1.20-1.93 (4H, m), 2.46 (3H, s), 3.00-3.13 (1H, m), 3.27-3.40 (1H, m), 3.69-3.90 (4H, m), 4.30 (2H, s), 7.45 (1H, m), 7.54-7.67 (3H, m), 8.40 (1H, d, J=8Hz), 8.55 (1H, d, J=8Hz)

Example 141

8-(2,6-Dichlorobenzoylamino)-3-[[N-(furan-2-yl-methyl)]-carbamoylmethyl]-2-methylimidazo[1,2-a]pyridine hydrochloride

mp : 231-233°C

NMR (DMSO-d_6, δ) : 2.46 (3H, s), 4.07 (2H, s), 4.28 (2H, d, J=7Hz), 6.26 (1H, d, J=3Hz), 6.40 (1H, t, J=3Hz), 7.48 (1H, m), 7.52-7.64 (4H, m), 8.52 (1H, d, J=8Hz), 8.60 (1H, d, J=8Hz), 8.72 (1H, t, J=7Hz)

Example 142

3-[(N-Cyclopentyl)carbamoylmethyl]-8-(2,6-dichlorobenzoylamino)-2-methylimidazo[1,2-a]pyridine hydrochloride

mp : >250°C

NMR (DMSO-d_6, δ) : 1.33-1.58 (4H, m), 1.60-1.70 (2H, m), 1.75-1.89 (2H, m), 2.48 (3H, s), 3.83-4.05 (3H, m), 7.50 (1H, m), 7.43-7.55 (3H, m), 8.31 (1H, d, J=8Hz), 8.50-8.61 (2H, m)

Example 143

8-(2,6-Dichlorobenzoylamino)-3-[(N,N-dimethylaminoacetylamino)phenyl]-2-trifluoromethylimidazo-[1,2-a]pyridine hydrochloride

mp : ~203°C

NMR ($CDCl_3$, δ) : 2.88 (3H, s), 2.90 (3H, s), 4.20 (2H, d, J=3Hz), 7.10 (1H, t, J=8Hz), 7.37 (1H, d, J=8Hz), 7.48-7.60 (3H, m), 7.63 (1H, t, J=8Hz),

7.80-7.89 (2H, m), 7.93 (1H, d, J=8Hz), 8.32 (1H, d, J=8Hz)

Example 144

3-[[N-(2-Aminophenyl)]carbamoylmethyl]-8-(2,6-dichlorobenzoylamino)-2-methylimidazo[1,2-a]pyridine hydrochloride

mp : -242°C

NMR (DMSO-d_6, δ) : 2.56 (3H, s), 4.36 (2H, s), 7.08 (1H, m), 7.12-7.22 (2H, m), 7.36 (1H, d, J=8Hz), 7.50-7.66 (4H, m), 8.66 (1H, d, J=8Hz), 8.80 (1H, d, J=8Hz), 10.40 (1H, br s), 11.56 (1H, br s)

Example 145

2-Carbamoyl-8-(2,6-dichlorobenzoylamino)-3-methylimidazo[1,2-a]pyridine

mp : >250°C

NMR (DMSO-d_6, δ) : 2.73 (3H, s), 7.05 (1H, t, J=8Hz), 7.40-7.48 (2H, m), 7.48-7.59 (3H, m), 8.14 (1H, d, J=8Hz), 8.20 (1H, d, J=8Hz)

Example 146

8-(2,6-Dichlorobenzoylamino)-2-methyl-3-[[N-(2-anilinophenyl)]carbamoylmethyl]imidazo[1,2-a]pyridine

mp : 224-226°C

NMR ($CDCl_3$, δ) : 1.82 (3H, s), 4.48 (2H, s), 6.77 (1H, t, J=8Hz), 6.99 (1H, d, J=8Hz), 7.10-7.14 (2H, m), 7.18-7.39 (7H, m), 7.46-7.53 (3H, m), 7.81 (1H, d, J=8Hz), 8.10 (1H, d, J=8Hz), 8.30 (1H, d, J=8Hz), 8.64 (1H, m)

Example 147

8-(2,6-Dichlorobenzoylamino)-3-[(N-methoxy-N-methyl)carbamoyl]methyl-2-methylimidazo[1,2-a]pyridine

mp : 169-171°C

NMR ($CDCl_3$, δ) : 2.42 (3H, s), 3.19 (3H, s), 3.67 (3H, s), 4.01 (2H, s), 6.85 (1H, t, J=8Hz), 7.28-7.40 (3H, m), 7.95 (1H, d, J=8Hz), 8.35 (1H, d, J=8Hz), 8.69 (1H, br s)

Example 148

8-(2,6-Dichlorobenzoylamino)-3-[[N-(2-methoxyethyl)]-carbamoylmethyl]imidazo[1,2-a]pyridine hydrochloride

mp : 218-220°C

NMR (DMSO-d_6, δ) : 3.21-3.28 (5H, m), 3.36 (2H, t, J=5Hz), 4.05 (2H, s), 7.47 (1H, m), 7.51-7.64 (3H, m), 8.02 (1H, s), 8.38 (1H, m), 8.50 (1H, d, J=8Hz), 8.54 (1H, d, J=8Hz)

Example 149

8-(2,6-Dichlorobenzoylamino)-2-methyl-3-[N-[(1S)-1-methoxycarbonylethyl]carbamoylmethyl]imidazo[1,2-a]pyridine hydrochloride

mp : 188-196°C

NMR (DMSO-d_6, δ) : 1.31 (3H, d, J=8Hz), 2.47 (3H, s), 4.07 (2H, m), 4.28 (1H, m), 7.40-7.70 (4H, m), 8.47 (1H, d, J=8Hz), 8.56 (1H, d, J=8Hz), 8.78 (1H, d, J=8Hz)

Example 150

8-(2,6-Dichlorobenzoylamino)-2-methyl-3-[[N-(2-morpholinoethyl)]carbamoylmethyl]imidazo[1,2-a]pyridine dihydrochloride

mp : 222-226°C

NMR (DMSO-d_6, δ) : 2.49 (3H, s), 3.00-3.30 (4H, m), 3.30-3.70 (4H, m), 3.80-4.00 (4H, m), 4.15 (2H, s), 7.40-7.70 (4H, m), 8.60-8.70 (2H, m), 8.75 (1H, d, J=8Hz)

Example 151

8-(2,6-Dichlorobenzoylamino)-2-methyl-3-[N-[(pyridin-3-yl)methyl]carbamoylmethyl]imidazo[1,2-a]pyridine dihydrochloride

mp : 180-189°C

NMR (DMSO-d_6, δ) : 2.49 (3H, s), 4.17 (1H, s), 4.45 (2H, d, J=7Hz), 7.40-7.70 (4H, m), 7.88 (1H, d, J=7.8Hz), 8.28 (1H, d, J=8Hz), 8.59 (1H, d, J=8Hz), 8.64 (1H, d, J=8Hz), 8.74 (1H, d, J=7Hz), 8.75 (1H, s), 9.03 (1H, t, J=7Hz)

Example 152

8-(2,6-Dichlorobenzoylamino)-2-methyl-3-(carbamoylmethyl)imidazo[1,2-a]pyridine hydrochloride

mp : 180-200°C

NMR (DMSO-d_6, δ) : 2.47 (3H, s), 3.97 (2H, s), 7.26 (1H, s), 7.40-7.70 (5H, m), 8.50 (1H, d, J=8Hz), 8.56 (1H, d, J=8Hz)

Example 153

8-(2,6-Dichlorobenzoylamino)-2-methyl-3-(N,N-dimethylcarbamoylmethyl)imidazo[1,2-a]pyridine hydrochloride

mp : >250°C

NMR (DMSO-d_6, δ) : 2.45 (3H, s), 2.88 (3H, s), 3.16 (3H, s), 4.28 (2H, s), 7.55 (1H, t, J=8Hz), 7.50-7.70 (3H, m), 8.42 (1H, d, J=8Hz), 8.57 (1H, d, J=8Hz)

Example 154

8-(2,6-Dichlorobenzoylamino)-3-[N-(2-methoxyethyl)-N-methylcarbamoyl]methyl-2-methylimidazo[1,2-a]pyridine hydrochloride

mp : 222-223°C

NMR (DMSO-d_6, δ) : 2.43 (9/5H, s), 2.47 (6/5H, s), 2.88 (9/5H, d, J=3Hz), 3.19 (6/5H, s), 3.26 (9/5H,

s), 3.38 (6/5H, d, J=3Hz), 3.40-3:25 (4H, m), 4.30 (4/5H, s), 4.33 (6/5H, s), 7.43-7.67 (4H, m), 8.30 (3/5H, d, J=8Hz), 8.39 (2/5H, d, J=8Hz), 8.58 (1H, d, J=8Hz)

Example 155

8-(2,6-Dichlorobenzoylamino)-2-methyl-3-[[N-(tetrahydrofuran-2-yl)methylcarbamoyl]methyl]imidazo-[1,2-a]pyridine hydrochloride

mp : >250°C

NMR (DMSO-d_6, δ) : 1.40-1.55 (1H, m), 1.71-1.94 (3H, m), 2.47 (3H, s), 3.05-3.23 (2H, m), 3.55-3.40 (3H, m), 4.03 (2H, s), 7.49 (1H, t, J=8Hz), 7.52-7.66 (3H, m), 8.38 (1H, t, J=6Hz), 8.53 (1H, d, J=8Hz), 8.59 (1H, d, J=8Hz)

Example 156

8-(2,6-Dichlorobenzoylamino)-2-methyl-3-[[N-(2-thienyl)methylcarbamoyl]methyl]imidazo[1,2-a]pyridine hydrochloride

mp : >250°C

NMR (DMSO-d_6, δ) : 2.46 (3H, s), 4.07 (2H, s), 4.44 (2H, d, J=6Hz), 6.94-6.99 (2H, m), 7.40 (1H, d, J=4Hz), 7.43-7.65 (4H, m), 8.51 (1H, d, J=8Hz), 8.59 (1H, d, J=8Hz), 8.84 (1H, t, J=6Hz)

Example 157

8-(2,6-Dichlorobenzoylamino)-2-methyl-3-[[N-(5-trifluoromethyl-1,3,4-thiadiazol-2-yl)]carbamoylmethyl]-imidazo[1,2-a]pyridine hydrochloride

mp : >250°C

NMR (DMSO-d_6, δ) : 2.50 (3H, s), 4.51 (2H, s), 7.47 (1H, t, J=8Hz), 7.52-7.65 (3H, m), 8.54-8.67 (2H, m)

Example 158

8-(2,6-Dichlorobenzoylamino)-2-methyl-3-[(N-piperidino)carbamoylmethyl]imidazo[1,2-a]pyridine dihydrochloride

mp : 178-191°C

NMR (DMSO-d_6, δ) : 1.40-1.80 (6H, m), 2.48 (2H, m), 3.05-3.15 (2H, m), 4.13-4.25 (2H, m), 7.50-7.65 (4H, m), 8.51-8.90 (2H, m)

Example 159

3-Bromo-2-carbamoyl-8-(2,6-dichlorobenzoylamino)-imidazo[1,2-a]pyridine

mp : >250°C

NMR ($CDCl_3$, δ) : 5.48-5.55 (2H, m), 7.10 (1H, t, J=8Hz), 7.22-7.30 (3H, m), 7.95 (1H, d, J=8Hz), 8.52 (1H, d, J=8Hz), 8.92 (1H, br s)

Example 160

A mixture of 8-(2,6-dichlorobenzoylamino)-3-hydroxymethyl-2-trifluoromethylimidazo[1,2-a]pyridine (100 mg), acetic anhydride (31 mg) and pyridine (40 mg) in dichloromethane (5 ml) was stirred at ambient temperature for 1 day. The reaction mixture was evaporated in vacuo and the residue was purified by column chromatography on silica gel. The obtained oil was crystallized from a mixture of ethyl acetate and hexane to give 3-acetoxymethyl-8-(2,6-dichlorobenzoylamino)-2-trifluoromethylimidazo[1,2-a]pyridine (85 mg).

mp : 191-193°C

NMR ($CDCl_3$, δ) : 2.10 (3H, s), 5.55 (2H, s), 7.08 (1H, t, J=7Hz), 7.30-7.45 (3H, m), 8.03 (1H, d, J=7Hz), 8.58 (1H, d, J=7Hz), 8.71 (1H, br s)

The following compound was obtained according to a similar manner to that of Example 160.

Example 161

3-Acetoxymethyl-8-(2,6-dichlorobenzoylamino)-2-methylimidazo[1,2-a]pyridine

mp : 210-213°C

NMR ($CDCl_3$, δ) : 2.06 (3H, s), 2.48 (3H, s), 5.40 (2H, s), 6.91 (1H, t, J=7Hz), 7.30-7.40 (3H, m), 7.91 (1H, d, J=7Hz), 8.41 (1H, d, J=7Hz), 8.73 (1H, br s)

Example 162

A mixture of 8-(2,6-dichlorobenzoylamino)-3-hydroxymethyl-2-trifluoromethylimidazo[1,2-a]pyridine (1.01 g), glutaric anhydride (342 mg), pyridine (257 mg) and 4-dimethylaminopyridine (10 mg) was stirred at ambient temperature overnight. The reaction mixture was washed with 1N-hydrochloric acid and brine, dried over sodium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel and the obtained oil was crystallized from diethyl ether to give 3-(4-carboxybutanoyloxymethyl)-8-(2,6-dichlorobenzoylamino)-2-trifluoromethylimidazo[1,2-a]pyridine (750 mg).

mp : 190-192°C

NMR ($CDCl_3$:CD_3OD = 20:1, δ) : 1.95 (2H quint., J=7Hz), 2.37 (2H, t, J=7Hz), 2.44 (2H, t, J=7Hz), 5.55 (2H, s), 7.13 (1H, t, J=8Hz), 7.33-7.45 (3H, m), 8.09 (1H, d, J=8Hz), 8.62 (1H, d, J=8Hz)

Example 163

A mixture of 8-(2,6-dichlorobenzoylamino)-3-hydroxymethyl-2-methylimidazo[1,2-a]pyridine (125 mg), acetic anhydride (55 mg) and pyridine (57 mg) in dichloromethane was stirred at ambient temperature overnight. The mixture was evaporated in vacuo and to the residue was added toluene. The mixture was evaporated in vacuo and the residue was dissolved in N,N-dimethylformamide (2 ml). To the solution

was added 4-hydroxypyridine (95 mg) and potassium carbonate (207 mg) and the mixture was stirred at 80°C for 2 hours. The mixture was cooled, poured into a mixture of ice and water and extracted with ethyl acetate. The extract was washed with brine, dried over sodium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel and the obtained oil was dissolved in methanolic hydrogen chloride. The solution was evaporated and the residue was crystallized from ethanol to give 8-(2,6-dichlorobenzoylamino)-2-methyl-3-(pyridin-4-yl)oxymethylimidazo[1,2-a]pyridine dihydrochloride (107 mg).

mp : 255-258°C

NMR (DMSO-d_6, δ) : 2.60 (3H, s), 6.14 (2H, s), 7.30-7.45 (3H, m), 7.50-7.60 (3H, m), 8.50-8.64 (4H, m)

Example 164

To a solution of 2-carbamoyl-8-(2,6-dichlorobenzoylamino)-3-methylimidazo[1,2-a]pyridine (2.5 g) in N,N-dimethylformamide (25 ml) was added thionylchloride (1.51 ml) dropwise. The mixture was stirred at ambient temperature for 2 hours and poured into water. The aqueous mixture was neutralized with aqueous saturated sodium bicarbonate. The separated solid was collected and washed with water to give 2-cyano-8-(2,6-dichlorobenzoylamino)-3-methylimidazo[1,2-a]pyridine (1.99 g).

mp : >250°C

NMR (DMSO-d_6, δ) : 2.64 (3H, s), 7.16 (1H, t, J=8Hz), 7.45-7.58 (3H, m), 8.22 (1H, d, J=8Hz), 8.28 (1H, d, J=8Hz)

Example 165

A mixture of 3-bromo-8-(2,6-dichlorobenzoylamino)-2-trifluoromethylimidazo[1,2-a]pyridine (136 mg), 4-mercaptopyridine (111 mg) and potassium carbonate (138 mg) in N,N-dimethylformamide (5 ml) was stirred at 120°C for 3

hours. The reaction mixture was cooled and poured into a mixture of ice and water and the separated oil was extracted with ethyl acetate. The extract was washed with brine, dried over sodium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel and the obtained oil was dissolved in methanolic hydrogen chloride. The solution was evaporated in vacuo and the residue was crystallized from ethyl acetate to give 8-(2,6-dichlorobenzoylamino)-3-(pyridin-4-yl)thio-2-trifluoromethylimidazo[1,2-a]pyridine hydrochloride (87 mg).

mp : 225-235°C

NMR (DMSO-d_6, δ) : 7.32 (1H, t, J=7Hz), 7.45-7.60 (5H, m), 8.33 (1H, d, J=7Hz), 8.52 (1H, d, J=7Hz), 8.58 (2H, d, J=6Hz)

Example 166

A mixture of 3-bromo-8-(2,6-dichlorobenzoylamino)-2-trifluoromethylimidazo[1,2-a]pyridine (500 mg), (trimethylsilyl)acetylene (420 mg), palladium chloride (20 mg), triphenylphosphine (58 mg), triethylamine (1.11 g) and copper iodide (26 mg) in acetonitrile (5 ml) was refluxed for 18 hours. The mixture was diluted with ethyl acetate, washed with brine, dried over sodium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel to give 8-(2,6-dichlorobenzoylamino)-2-trifluoromethyl-3-[(trimethylsilyl)ethynyl]imidazo[1,2-a]-pyridine (amorphous, 70 mg).

NMR ($CDCl_3$, δ) : 0.32 (9H, s), 7.10 (1H, t, J=8Hz), 7.32-7.42 (3H, m), 8.07 (1H, d, J=8Hz), 8.59 (1H, d, J=8Hz), 8.66 (1H, m)

Example 167

Tetrabutylammonium fluoride (1.0M solution in tetrahydrofuran, 0.016 ml) was added to a solution of 8-(2,6-dichlorobenzoylamino)-2-trifluoromethyl-3-[(trimethylsilyl)-

ethynyl]imidazo[1,2-a]pyridine (65 mg) in tetrahydrofuran (1 ml) at 4°C. The mixture was stirred at ambient temperature for 30 minutes and evaporated in vacuo. The residue was purified by column chromatography on silica gel and the obtained oil was crystallized from a mixture of ethanol and water to give 3-ethynyl-8-(2,6-dichlorobenzoylamino)-2-trifluoromethylimidazo[1,2-a]pyridine (31 mg).

mp. 190-194°C

NMR ($CDCl_3$, δ) : 3.45 (1H, s), 7.12 (1H, t, J=8Hz), 7.33-7.43 (3H, m), 8.11 (1H, d, J=8Hz), 8.61 (1H, d, J=8Hz), 8.68 (1H, br s)

Example 168

A mixture of 8-(2,6-dichlorobenzoylamino)-3-(1,4-dihydro-1-methoxycarbonylpyridin-4-yl)-2-methylimidazo-[1,2-a]pyridine (300 mg), sodium iodide (147 mg) and tetrabutylammonium hydrogen sulfate (22 mg) in dimethyl sulfoxide (4 ml) was stirred at 120°C for 8 hours. The mixture was cooled and poured into water. The separated solid was collected, dried in vacuo and purified by column chromatography on silica gel. The obtained crystalline was triturated with ethanol and dissolved in methanolic hydrogen chloride. The solution was evaporated in vacuo and the residue was crystallized from ethanol to give 8-(2,6-dichlorobenzoylamino)-2-methyl-3-(pyridin-4-yl)imidazo-[1,2-a]pyridine hydrochloride (103 mg).

mp : 255-260°C

NMR ($CDCl_3$:CD_3OD = 20:1, δ) : 2.73 (3H, s), 7.37-7.44 (3H, m), 7.50 (1H, m), 8.10-8.16 (2H, m), 8.45 (1H, m), 9.02-9.10 (2H, m), 9.12 (1H, d, J=8Hz)

Example 169

Hydrogen peroxide (30%, 0.95 ml) was added to a mixture of 3-cyanomethyl-8-(2,6-dichlorobenzoylamino)-2-methylimidazo[1,2-a]pyridine (100 mg) and aqueous sodium

hydroxide (1N, 0.66 ml) in ethanol (2 ml). The mixture was stirred at ambient temperature for 30 minutes and neutralized with 1N-hydrochloric acid. The mixture was extracted with ethyl acetate. The extract was washed with aqueous saturated sodium bicarbonate and brine, dried over sodium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel and the obtained oil was crystallized from diisopropyl alcohol to give 3-carbamoylmethyl-8-(2,6-dichlorobenzoylamino)-2-methylimidazo[1,2-a]pyridine (27 mg).

mp : >250°C

NMR (DMSO-d_6, δ) : 2.32 (3H, s), 3.78 (3H, s), 6.89 (1H, t, J=8Hz), 7.08 (1H, br s), 7.41-7.54 (3H, m), 8.06 (2H, t, J=8Hz)

Example 170

A mixture of 3-bromo-8-(2,6-dichlorobenzoylamino)-2-trifluoromethylimidazo[1,2-a]pyridine (300 mg), phenylboric acid (121 mg) and tetrakis(triphenylphosphine)palladium (15 mg) in a mixture of aqueous sodium carbonate (2M, 1.7 ml) and 1,2-dimethoxyethane (3 ml) was refluxed for 3 hours. The mixture was partitioned between ethyl acetate and aqueous saturated sodium bicarbonate. The organic layer was separated, washed with brine, dried over sodium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel and the obtained oil was crystallized from diisopropyl ether to give 8-(2,6-dichlorobenzoylamino)-3-phenyl-2-trifluoromethylimidazo-[1,2-a]pyridine (116 mg).

mp : -139°C

NMR ($CDCl_3$, δ) : 6.93 (1H, t, J=8Hz), 7.33-7.44 (3H, m), 7.44-7.51 (2H, m), 7.51-7.60 (3H, m), 7.73 (1H, d, J=8Hz), 8.52 (1H, d, J=8Hz), 8.84 (1H, br s)

Example 171

To a solution of sodium carbonate (81 mg) in water (0.5 ml) was added hydroxylamine hydrochloride (53 mg), ethanol (7 ml) and 3-cyanomethyl-8-(2,6-dichlorobenzoylamino)-2-methylimidazo[1,2-a]pyridine (230 mg). The mixture was refluxed for 6 hours and poured into water. The separated solid was collected, washed with water and dried. The solid was dissolved in 4N-hydrogen chloride in ethyl acetate and the solution was evaporated in vacuo. The residue was crystallized from a mixture of diisopropyl alcohol and ethyl acetate to give 8-(2,6-dichlorobenzoylamino)-3-(N-hydroxyamidino)methyl-2-methylimidazo[1,2-a]pyridine hydrochloride (169 mg).

mp : 196-198°C

NMR (DMSO-d_6, δ) : 2.50 (3H, s), 4.46 (2H, s), 7.45-7.63 (4H, m), 8.50 (1H, m), 8.69 (1H, m), 8.83 (1H, br s), 11.10 (1H, br s), 11.78 (1H, br s)

Example 172

Acetic anhydride (21 mg) was added to a mixture of 8-(2,6-dichlorobenzoylamino)-3-(N-hydroxyamidino)methyl-2-methylimidazo[1,2-a]pyridine hydrochloride (80 mg) and sodium acetate (15 mg) in acetic acid (1 ml). The mixture was stirred at ambient temperature for 30 minutes and at 80°C for 5 hours. The mixture was evaporated in vacuo and the residue was partitioned between ethyl acetate and aqueous saturated sodium bicarbonate. The organic layer was separated, dried over sodium sulfate and evaporated in vacuo. The residue was purified by preparative TLC and the obtained oil was crystallized from diethyl ether to give 8-(2,6-dichlorobenzoylamino)-2-methyl-3-(5-methyl-1,2,4-oxadiazol-3-yl)methylimidazo[1,2-a]pyridine (18 mg).

mp : 215-216°C

NMR ($CDCl_3$, δ) : 2.49 (3H s), 2.53 (3H, s), 4.28 (2H, s), 6.87 (1H, t, J=8Hz), 7.28-7.40 (3H, m), 7.88

(1H, d, J=8Hz), 8.37 (1H, d, J=8Hz), 8.72 (1H, m)

Example 173

A solution of 3-acetoxymethyl-8-(2,6-dichlorobenzoylamino)-2-methylimidazo[1,2-a]pyridine (100 mg) in methanol (5 ml) was refluxed for 5 hours. The reaction mixture was evaporated in vacuo and the residue was crystallized from diethyl ether to give 8-(2,6-dichlorobenzoylamino)-3-methoxymethyl-2-methylimidazo-[1,2-a]pyridine (72 mg).

mp : 178-180°C

NMR ($CDCl_3$, δ) : 2.45 (3H, s), 3.33 (3H, s), 4.72 (2H, s), 6.88 (1H, t, J=7Hz), 7.30-7.40 (3H, m), 7.90 (1H, d, J=7Hz), 8.40 (1H, d, J=7Hz), 8.69 (1H, br s)

Example 174

A mixture of 3-bromo-2-carbamoyl-8-(2,6-dichlorobenzoylamino)imidazo[1,2-a]pyridine (200 mg) and thionyl chloride (1 ml) in 1,4-dioxane was refluxed for 8 hours. The mixture was cooled and poured into a mixture of ice and water. The mixture was neutralized with aqueous saturated sodium bicarbonate and extracted with ethyl acetate. The extract was washed with aqueous saturated sodium bicarbonate and brine, dried over sodium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel and the obtained oil was crystallized from diethyl ether to give 3-bromo-2-cyano-8-(2,6-dichlorobenzoylamino)imidazo[1,2-a]pyridine (33 mg).

mp : >250°C

NMR ($CDCl_3$:CD_3OD = 20:1, δ) : 7.20 (1H, t, J=8Hz), 7.35-7.46 (3H, m), 7.94 (1H, d, J=8Hz), 8.62 (1H, d, J=8Hz)

Example 175

4-Hydroxypyridine (95 mg) was added to a suspension of sodium hydride (24 mg) in N,N-dimethylformamide (3 ml) at 4°C. The mixture was stirred at ambient temperature for 30 minutes and to the mixture was added cuprous oxide (108 mg) and 3-bromo-8-(2,6-dichlorobenzoylamino)-2-methylimidazo-[1,2-a]pyridine (200 mg). The mixture was stirred at 100°C for 5 hours, cooled and poured into a mixture of ice and water. The separated oil was extracted with ethyl acetate and the extract was washed with brine, dried over sodium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel and the obtained oil was crystallized from diethyl ether to give 3-bromo-8-[2-chloro-6-(pyridin-4-yl)oxybenzoylamino]-2-methylimidazo[1,2-a]-pyridine (110 mg).

mp : 177-178°C

NMR ($CDCl_3$, δ) : 2.49 (3H, s), 6.66 (1H, d, J=7Hz), 6.90 (1H, d, J=7Hz), 7.00-7.10 (3H, m), 7.12 (1H, t, J=7Hz), 7.27 (1H, d, J=7Hz), 8.11 (1H, d, J=7Hz), 8.38 (2H, d, J=5Hz)

The following comounds (Examples 176 to 177) were obtained according to a similar manner to that of Preparation 22.

Example 176

8-(2,6-Dichlorobenzoylamino)-3-(1-hydroxy-1-methylethyl)-2-trifluoromethylimidazo[1,2-a]pyridine

mp : 220-222°C

NMR (DMSO-d_6, δ) : 1.68 (6H, s), 5.91 (1H, s), 7.09 (1H, t, J=7Hz), 7.45-7.60 (3H, m), 8.18 (1H, d, J=7Hz), 8.92 (1H, d, J=7Hz)

Example 177

8-(2,6-Dichlorobenzoylamino)-3-(1-hydroxy-1-methylethyl)-2-methylimidazo[1,2-a]pyridine

mp : 248°C (dec.)

NMR ($CDCl_3$:CD_3OD = 20:1, δ) : 1.77 (6H, s), 2.49 (3H, s), 6.81 (1H, t, J=8Hz), 7.31-7.43 (3H, m), 8.38 (1H, d, J=8Hz), 8.60 (1H, d, J=8Hz)

Example 178

A mixture of 3-[[N-(2-aminophenyl)]carbamoylmethyl]-8-(2,6-dichlorobenzoylamino)-2-methylimidazo[1,2-a]pyridine hydrochloride (120 mg) and 10% hydrogenchloride in methanol (0.3 ml) in ethanol (3 ml) was refluxed for 8 hours. After evaporation in vacuo, the obtained residue was crystallized from ethanol to give 3-[(1H-benzimidazol-2-yl)methyl]-8-(2,6-dichlorobenzoylamino)-2-methylimidazo[1,2-a]pyridine dihydrochloride (34 mg).

mp : >250°C

NMR (DMSO-d_6, δ) : 2.55 (3H, s), 5.15 (2H, s), 7.41 (1H, m), 7.46-7.53 (2H, m), 7.53-7.64 (3H, m), 7.71 (2H, dd, J=3Hz and 8Hz), 8.60 (1H, m), 8.67 (1H, m)

Example 179

A mixture of 8-(2,6-dichlorobenzoylamino)-3-hydroxymethyl-2-trifluoromethylimidazo[1,2-a]pyridine (162 mg) and triethylsilane (464 mg) in trifluoroacetic acid (2 ml) was stirred at ambient temperature for 2 days. The reaction mixture was evaporated in vacuo and partitioned between dichloromethane and aqueous saturated sodium bicarbonate. The organic layer was separated, dried over sodium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel and the obtained oil was crystallized from a mixture of diethyl ether and diisopropyl ether to give 8-(2,6-dichlorobenzoylamino)-3-methyl-2-trifluoromethylimidazo[1,2-a]pyridine (84 mg).

mp : 248-250°C

NMR ($CDCl_3$, δ) : 2.62 (3H, s), 7.01 (1H, t, J=8Hz), 7.30-7.43 (3H, m), 7.71 (1H, d, J=8Hz), 8.48 (1H, d, J=8Hz), 8.75 (1H, br s)

Example 180

A mixture of 3-(4-carboxybutanoyloxymethyl)-8-(2,6-dichlorobenzoylamino)-2-trifluoromethylimidazo[1,2-a]pyridine (700 mg), disuccinimidyl carbonate (1.04 g) and pyridine (380 mg) in acetonitrile (50 ml) was stirred at ambient temperature overnight. The reaction mixture was evaporated in vacuo. The residue was dissolved in ethyl acetate and the insoluble solid was filtered. The filtrate was washed with aqueous saturated sodium bicarbonate, dried over sodium sulfate and evaporated in vacuo to give 8-(2,6-dichlorobenzoylamino)-3-(4-succinimidoxycarbonyl-butanoyloxymethyl)-2-trifluoromethylimidazo[1,2-a]pyridine (amorphous, 933 mg).

NMR ($CDCl_3$, δ) : 2.08 (2H, quint., J=7Hz), 2.50 (2H, t, J=7Hz), 2.71 (2H, t, J=7Hz), 2.83 (4H, s), 5.57 (2H, s), 7.09 (1H, t, J=8Hz), 7.30-7.45 (3H, m), 8.05 (1H, d, J=8Hz), 8.57 (1H, d, J=8Hz), 8.72 (1H, br s)

Example 181

A mixture of 8-(2,6-dichlorobenzoylamino)-3-(4-succinimidoxycarbonylbutanoyloxymethyl)-2-trifluoromethylimidazo[1,2-a]pyridine (123 mg), aminomethylenebis(phosphonic acid) (77 mg) and triethylamine (162 mg) in N,N-dimethylformamide (3 ml) and water (0.5 ml) was stirred at ambient temperature for 3 hours. To the mixture was added 1N-hydrochloric acid (1.6 ml) and the mixture was evaporated in vacuo. Azeotropic evaporation of the residue with ethanol was repeated 3 times and the residual gum was washed by decantation with hot ethyl acetate

3 times. The residue was solidified from diisopropyl ether, collected and washed with a small amount of water to give 4-[[8-(2,6-dichlorobenzoylamino)-2-trifluoromethylimidazo-[1,2-a]pyridin-1-yl]methoxycarbonyl]-butanoylaminomethylenebis(phosphonic acid) (25 mg)

NMR (DMSO-d_6, δ) : 1.73 (2H, quint., J=7Hz), 2.21 (2H, t, J=7Hz), 2.34 (2H, t, J=7Hz), 4.46 (1H, dt, J=9Hz and 20Hz), 5.57 (2H, s), 7.23 (1H, t, J=8Hz), 7.45-7.60 (3H, m), 8.32 (1H, d, J=8Hz), 8.45 (1H, d, J=8Hz)

FAB-MASS : 691 $(M+H)^+$, 713 $(M+Na)^+$

Example 182

m-Chloroperbenzoic acid (55 mg) was added to a solution of 8-(2,6-dichlorobenzoylamino)-3-(1-methylimidazol-2-yl)thiomethyl-2-trifluoromethylimidazo[1,2-a]pyridine (102 mg) in dichloromethane (5 ml) at 4°C. The mixture was stirred at ambient temperature for 5 hours, washed with aqueous sodium thiosulfate (5%), aqueous saturated sodium bicarbonate and brine. The organic layer was dried over sodium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel. The first fractions were evaporated in vacuo and the residue was crystallized from diethyl ether to give 8-(2,6-dichlorobenzoylamino)-3-(1-methylimidazol-2-yl)-sulfonylmethyl-2-trifluoromethylimidazo[1,2-a]pyridine (35 mg).

mp : 223-224°C

NMR (DMSO-d_6, δ) : 3.74 (3H, s), 5.52 (2H, s), 7.13 (1H, s), 7.18 (1H, t, J=8Hz), 7.45-7.60 (4H, m), 8.32 (1H, d, J=8Hz), 8.40 (1H, d, J=8Hz)

The second fractions were evaporated in vacuo and the residue was crystallized from diethyl ether to give 8-(2,6-dichlorobenzoylamino)-3-(1-methylimidazol-2-yl)-

sulfinylmethyl-2-trifluoromethylimidazo[1,2-a]pyridine

mp : 194-195°C

NMR (DMSO-d_6, δ) : 3.77 (3H, s), 5.12 (1H, d, J=15Hz), 5.38 (1H, d, J=15Hz), 7.15 (1H, s), 7.15 (1H, t, J=8Hz), 7.45 (1H, s), 7.45-7.60 (3H, m), 8.31 (1H, d, J=8Hz), 8.48 (1H, d, J=8Hz)

Example 183

A mixture of 8-(2,6-dichlorobenzoylamino)-2-methyl-3-nitroimidazo[1,2-a]pyridine (400 mg), iron (302 mg) and acetic acid (2 ml) in a mixture of tetrahydrofuran (4 ml) and ethanol (8 ml) was refluxed for 2 hours. After filtration of insoluble materials, the obtained filtrate was evaporated with toluene in vacuo. The residue was partitioned between ethyl acetate and aqueous saturated sodium bicarbonate. The organic layer was separated, dried over sodium sulfate and evaporated in vacuo to give a crude solid. The solid was dissolved in hot methanol and the solution was filtered. The filtrate was treated with excessive 10% hydrogen chloride in methanol and evaporated in vacuo. The obtained solid was triturated with hot isopropyl alcohol to give 3-amino-8-(2,6-dichlorobenzoylamino)-2-methylimidazo[1,2-a]pyridine hydrochloride (153 mg).

mp : 262°C (dec.)

NMR (DMSO-d_6, δ) : 5.43-5.72 (2H, m), 7.43 (1H, t, J=8Hz), 7.52-7.64 (3H, m), 8.31 (1H, d, J=8Hz), 8.48 (1H, d, J=8Hz)

Example 184

A mixture of 3-acetyl-8-(2,6-dichlorobenzoylamino)-2-methylimidazo[1,2-a]pyridine (125 mg) and sodium borohydride in methanol (3 ml) was stirred at ambient temperature for 3 hours. To the reaction mixture was added water and the separated solid was collected and washed with water to give 8-(2,6-dichlorobenzoylamino)-3-(1-hydroxyethyl)-2-

methylimidazo[1,2-a]pyridine (105 mg).

mp : 206-210°C

NMR ($CDCl_3$, δ) : 1.59 (3H, d, J=7Hz), 2.26 (3H, s), 3.27 (1H, br s), 5.32 (1H, q, J=7Hz), 6.80 (1H, t, J=7Hz), 7.20-7.35 (3H, m), 8.20 (1H, d, J=7Hz), 8.35 (1H, d, J=7Hz), 8.94 (1H, br s)

Example 185

Sodium cyanoborohydride (183 mg) was added portionwise to a mixture of 3-(3-aminophenyl)-8-(2,6-dichlorobenzoylamino)-2-trifluoromethylimidazo[1,2-a]pyridine (150 mg) and 37% formaldehyde in water (522 mg) in tetrahydrofuran (2 ml) and methanol (1.5 ml) at ambient temperature with stirring. During the reaction period of 3 hours, the mixture was kept to pH 3 by addition of 1N-hydrochloric acid. After brought to pH 2 with 1N-hydrochloric acid, the mixture was made alkaline with aqueous saturated sodium bicarbonate. The separated oil was extracted with ethyl acetate and the extract was washed with aqueous saturated sodium bicarbonate and brine. The organic layer was dried over sodium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel and the obtained oil was crystallized from a mixture of ethanol and water to give 8-(2,6-dichlorobenzoylamino)-3-(3-dimethylaminophenyl)-2-trifluoromethylimidazo[1,2-a]pyridine (93 mg).

mp : 204-205°C

NMR ($CDCl_3$, δ) : 3.00 (6H, s), 6.72-6.80 (2H, m), 6.84-6.93 (2H, m), 7.33-7.44 (4H, m), 7.80 (1H, d, J=8Hz), 8.50 (1H, d, J=8Hz), 8.82 (1H, br s)

Example 186

A mixture of 3-cyanomethyl-8-(2,6-dichlorobenzoylamino)imidazo[1,2-a]pyridine (773 mg) and 1N aqueous sodium hydroxide (5 ml) in ethanol (7 ml) was stirred

for 6 hours at 90°C. After cooling to ambient temperature, the mixture was neutralized with 1N-hydrochloric acid. The separated solid was collected and washed with water to give 3-carboxymethyl-8-(2,6-dichlorobenzoylamino)imidazo[1,2-a]-pyridine (451 mg).

mp : >250°C

NMR (DMSO-d_6, δ) : 4.04 (2H, s), 6.95 (1H, t, J=8Hz), 7.42-7.55 (4H, m), 8.10 (1H, d, J=8Hz), 8.12 (1H, d, J=8Hz),

ESI-MASS : 364 (M^++1)

Example 187

Sodium cyanoborohydride (33 mg) was added portionwise to a mixture of 3-(3-aminophenyl)-8-(2,6-dichlorobenzoylamino)-2-trifluoromethylimidazo[1,2-a]pyridine (150 mg) and 2-furaldehyde (34 mg) in methanol (3 ml) at ambient temperature with stirring. During the reaction period of 2 hours, the mixture was kept to pH 3 by addition of 1N-hydrochloric acid. After brought to pH 2 with 1N-hydrochloric acid, the residue was made alkaline with aqueous saturated sodium bicarbonate. The separated oil was extracted with ethyl acetate and the extract was washed with aqueous saturated sodium bicarbonate. The organic layer was dried over sodium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel and the obtained oil was crystallized from a mixture of ethanol and water to give 8-(2,6-dichlorobenzoylamino)-3-[3-(furan-2-yl)methylamino]phenyl]-2-trifluoromethylimidazo[1,2-a]pyridine (141 mg).

mp : 211-213°C

NMR ($CDCl_3$, δ) : 4.28 (1H, m), 4.36 (2H, d, J=7Hz), 6.26 (1H, d, J=3Hz), 6.37 (1H, d, J=3Hz), 6.72 (1H, m), 6.80-6.85 (2H, m), 6.90 (1H, t, J=8Hz), 7.31-7.44 (5H, m), 7.73 (1H, d, J=8Hz), 8.50 (1H, d, J=8Hz), 8.81 (1H, br s)

Example 188

Sodium hydride (60%, 48 mg) was added to a solution of 3-chloro-8-(2,6-dichlorobenzoylamino)-2-methylimidazo-[1,2-a]pyridine (354 mg) in N,N-dimethylformamide (7 ml). The mixture was stirred at ambient temperature for 30 minutes and methyl iodide (710 mg) was added to the mixture. After stirring at ambient temperature for 1 hour, the mixture was partitioned between dichloromethane and water. The organic layer was separated, washed with water, dried over sodium sulfate and evaporated in vacuo. The residue was dissolved in diethyl ether and the solution was extracted with 1N-hydrochloric acid. The aqueous solution was neutralized with aqueous saturated sodium bicarbonate and extracted with dichloromethane. The extract was dried over sodium sulfate and evaporated in vacuo. The residue was crystallized from a mixture of diethyl ether and hexane to give 3-chloro-8-[N-(2,6-dichlorobenzoyl)]methylamino-2-methylimidazo[1,2-a]-pyridine (217 mg).

mp : 138-139°C

The following compounds (Examples 189 to 194) were obtained according to a similar manner to that of Example 12.

Example 189

8-(2,6-Dichlorobenzoylamino)-2,3-dimethylimidazo-[1,2-a]pyridine hydrochloride

mp : >250°C

NMR ($CDCl_3$, δ) : 2.50 (3H, s), 2.56 (3H, s), 7.25-7.45 (4H, m), 7.87 (1H, d, J=7Hz), 9.03 (1H, d, J=7Hz)

Example 190

8-(2-Chloro-6-methylbenzoylamino)-3-hydroxymethyl-2-trifluoromethylimidazo[1,2-a]pyridine hydrochloride

mp : 168-173°C

NMR ($CDCl_3$:CD_3OD = 9:1, δ) : 2.37 (3H, s), 4.99 (2H,

s), 7.10-7.25 (4H, m), 8.28 (1H, d, J=7Hz), 8.73 (1H, d, J=7Hz)

Example 191

8-(2,6-Dichlorobenzoylamino)-3-(1-hydroxy-1-methylethyl)-2-methylimidazo[1,2-a]pyridine hydrochloride

mp : 248-250°C

NMR (DMSO-d_6, δ) : 1.20 (6H, S), 2.58 (3H,S), 7.45 (1H, t, J=7Hz), 7.50-7.65 (3H, m), 8.63 (1H, d, J=7Hz), 9.00 (1H, d, J=7Hz)

Example 192

8-(2,6-Dichlorobenzoylamino)-3-(1-hydroxy-1-methylethyl)-2-trifluoromethylimidazo[1,2-a]pyridine hydrochloride

mp : 134-137°C

NMR (DMSO-d_6, δ) : 1.68 (6H, s), 7.08 (1H, t, J=7Hz), 7.45-7.60(3H, m), 8.18 (1H, d, J=7Hz), 8.91 (1H, d, J=7Hz)

Example 193

8-(2,6-Dichlorobenzoylamino)-3-methoxy-2-methylimidazo[1,2-a]pyridine hydrochloride

mp : 191-193°C

NMR ($CDCl_3$, δ) : 2.60 (3H, m), 4.13 (3H, m), 7.28-7.41 (4H, m), 7.92 (1H, d, J=8Hz), 9.00(1H, d, J=8Hz)

Example 194

8-(2,6-Dichlorobenzoylamino)-3-(1-methylimidazol-2-yl)thiomethyl-2-trifluoromethylimidazo[1,2-a]pyridine hydrochloride

mp : 155-165°C

NMR (DMSO-d_6, δ) : 3.69(3H, s), 4.83(2H, s), 7.28(1H, s), 7.45-7.57(3H, m), 7.72(1H, s), 7.87(1H, s), 8.88(1H, d, J=8Hz), 8.58(1H, d, J=8Hz)

Example 195

To a suspension of 8-(2,6-dichlorobenzoylamino)-3-hydroxymethyl-2-trifluoromethylimidazo[1,2-a]pyridine (20.0 g) in dichloromethane (400 ml) was added thionyl chloride (7.2 ml) and pyridine (1 ml) dropwise. The mixture was stirred for two and half hours at ambient temperature. The reaction mixture was evaporated under reduced pressure and the residue was diluted with toluene (200 ml) and evaporated under reduced pressure three times. The residual solid was triturated with diethyl ether (200 ml) to give 3-chloromethyl-8-(2,6-dichlorobenzoylamino)-2-trifluoromethyl-imidazo[1,2-a]pyridine (20.4 g) as a pale yellow solid.

mp : 200-203°C

NMR ($CDCl_3$, δ) : 5.05 (2H, s), 7.17 (3H, t, J=8Hz), 7.30-7.45 (3H, m), 7.98 (1H, d, J=8Hz), 8.62 (1H, d, J=8Hz), 8.73 (1H, s)

Example 196

To a solution of potassium cyanide (925 mg) in water (7 ml) was added acetonitrile (30 ml) and 3-chloromethyl-8-(2,6-dichlorobenzoylamino)-2-trifluoromethylimidazo[1,2-a]pyridine (3.0 g). The mixture was stirred for 20 minutes at 45°C and then diluted with water (30 ml). The mixture was stirred for 30 minutes in an ice bath and the precipitate was filtered and washed with water to give 3-cyanomethyl-8-(2,6-dichlorobenzoylamino)-2-trifluoromethylimidazo[1,2-a]pyridine (1.9 g).

mp : 210-213°C

NMR ($CDCl_3$, δ) : 4.21 (2H, s), 7.19 (1H, t, J=8Hz), 7.32-7.47 (3H, m), 7.90 (1H, d, J=8Hz), 8.64 (1H, d, J=8Hz), 8.70 (1H, s)

The following compound was obtained according to a similar manner to that of Example 186.

Example 197

3-Carboxymethyl-8-(2,6-dichlorobenzoylamino)-2-trifluoromethylimidazo[1,2-a]pyridine

mp : >250°C

NMR (DMSO-d_6, δ) : 4.22 (2H, s), 7.16 (1H, t, J=8Hz), 7.44-7.58 (3H, m), 8.28 (1H, d, J=8Hz), 8.38 (1H, d, J=8Hz)

The following compounds [Examples 198 to 212] were obtained according to a similar manner to that of Example 10.

Example 198

3-Carbamoylmethyl-8-(2,6-dichlorobenzoylamino)-2-trifluoromethylimidazo[1,2-a]pyridine

mp : >260°C

NMR ($CDCl_3$, δ) : 4.01 (2H, s), 7.07 (1H, t, J=8Hz), 7.35-7.45 (3H, m), 8.00 (1H, d, J=8Hz), 8.58 (1H, d, J=8Hz)

Example 199

3-(N-Cyanomethylcarbamoylmethyl)-8-(2,6-dichlorobenzoylamino)-2-trifluoromethylimidazo[1,2-a]pyridine

mp : 248-251°C

NMR ($CDCl_3$, δ) : 4.05 (2H, s), 4.12 (2H, s), 7.09 (1H, t, J=8Hz), 7.33-7.46 (3H, m), 8.01 (1H, d, J=8Hz), 8.60 (1H, d, J=8Hz)

Example 200

8-(2,6-Dichlorobenzoylamino)-3-[N-(2-hydroxyethyl)-carbamoylmethyl]-2-trifluoromethylimidazo[1,2-a]pyridine

mp : 239-241°C

NMR ($CDCl_3$, δ) : 3.35 (2H, t, J=5Hz), 3.63 (2H, t, J=5Hz), 4.00 (2H, s), 7.05 (1H, t, J=8Hz), 7.32-7.45 (3H, m), 8.05 (1H, d, J=8Hz), 8.58 (1H, d, J=8Hz)

ESI-MASS : 475 (M^++1)

Example 201

8-(2,6-Dichlorobenzoylamino)-3-[N-(2-methoxyethyl)-carbamoylmethyl]-2-trifluoromethylimidazo[1,2-a]pyridine

mp : 184-186°C

NMR ($CDCl_3$, δ) : 3.31 (3H, s), 3.98 (2H, s), 5.98 (1H, br s), 7.05 (1H, t, J=8Hz), 7.32-7.45 (3H, m), 8.08 (1H, d, J=8Hz), 8.54 (1H, d, J=8Hz), 8.70 (1H, s)

ESI-MASS : 489 (M^++1)

Example 202

8-(2,6-Dichlorobenzoylamino)-3-[N-(pyridin-3-yl)-carbamoylmethyl]-2-trifluoromethylimidazo[1,2-a]pyridine

mp : 236-238°C

NMR (DMSO-d_6, δ) : 4.39 (2H, s), 7.14 (1H, t, J=8Hz), 7.30-7.40 (1H, m), 7.42-7.58 (3H, m), 8.01 (1H, d, J=8Hz), 8.24-8.32 (2H, m), 8.41 (1H, d, J=8Hz), 8.73 (1H, s)

Example 203

8-(2,6-Dichlorobenzoylamino)-3-[N-(2-aminopyridin-3-yl)-carbamoylmethyl]-2-trifluoromethylimidazo[1,2-a]pyridine

mp : 240-243°C

NMR ($CDCl_3$, δ) : 4.20 (2H, s), 6.72 (1H, dd, J=8Hz and 4Hz), 7.07 (1H, t, J=8Hz), 7.30-7.47 (3H, m), 7.57 (1H, d, J=8Hz), 7.95 (1H, d, J=8Hz), 8.10 (1H, d, J=8Hz), 8.60 (1H, d, J=8Hz)

ESI-MASS : 523.1 (M^++1)

Example 204

8-(2,6-Dichlorobenzoylamino)-3-(N-furfurylcarbamoyl-methyl)-2-trifluoromethylimidazo[1,2-a]pyridine

mp : 180-183°C

NMR ($CDCl_3$, δ) : 4.00 (2H, s), 4.41 (2H, d, J=6Hz),

5.91 (1H, br), 6.19 (1H, d, J=4Hz), 6.30 (1H, d, J=4Hz), 7.03 (1H, t, J=8Hz), 7.33 (1H, s), 7.34-7.44 (3H, m), 8.05 (1H, d, J=8Hz), 8.54 (1H, d, J=8Hz), 8.73 (1H, s)

Example 205

8-(2,6-Dichlorobenzoylamino)-3-[N-[2-(imidazol-4-yl)-ethyl]carbamoylmethyl]-2-trifluoromethylimidazo[1,2-a]-pyridine hydrochloride

mp : 180-190°C

NMR (DMSO-d_6, δ) : 2.82 (2H, t, J=6Hz), 3.40 (2H, q, J=6Hz), 4.07 (2H, s), 7.12 (1H, t, J=8Hz), 7.44 (1H, s), 7.45-7.58 (3H, m), 8.22 (1H, d, J=8Hz), 8.26 (1H, d, J=8Hz), 8.76 (1H, t, J=6Hz), 9.01 (1H, s)

Example 206

8-(2,6-Dichlorobenzoylamino)-3-[N-(pyridin-2-yl)-carbamoylmethyl]-2-trifluoromethylimidazo[1,2-a]pyridine hydrochloride

mp : 238-240°C

NMR (DMSO-d_6, δ) : 4.48 (2H, s), 7.10-7.20 (2H, m), 7.46-7.57 (3H, m), 7.85 (1H, t, J=8Hz), 7.95 (1H, d, J=8Hz), 8.78 (1H, d, J=8Hz), 8.37 (1H, d, J=8Hz), 8.42 (1H, d, J=8Hz)

Example 207

8-(2,6-Dichlorobenzoylamino)-3-[[N-(pyridin-2-yl)-methyl]carbamoylmethyl]-2-trifluoromethylimidazo[1,2-a]-pyridine hydrochloride

mp : >250°C

NMR ($CDCl_3$, δ) : 4.09 (2H, s), 4.53 (2H, d, J=5Hz), 6.98-7.23 (4H, m), 7.29-7.45 (3H, m), 7.67 (1H, t, J=8Hz), 8.09 (1H, d, J=8Hz), 8.45-8.55 (2H, m), 8.74 (1H, s)

ESI-MASS : 522 (M^++1)

Example 208

8-(2,6-Dichlorobenzoylamino)-3-[[N-(pyridin-3-yl)-methyl]carbamoylmethyl]-2-trifluoromethylimidazo[1,2-a]-pyridine hydrochloride

mp : 167-180°C

NMR (DMSO-d_6, δ) : 4.21 (2H, s), 4.50 (2H, d, J=6Hz), 7.12 (1H, t, J=8Hz), 7.40-7.57 (3H, m), 8.05 (1H, t, J=8Hz), 8.25 (1H, d, J=8Hz), 8.37 (1H, d, J=8Hz), 8.46 (1H, d, J=8Hz), 8.83 (1H, s), 9.12 (1H, s)

Example 209

8-(2,6-Dichlorobenzoylamino)-3-[[N-(pyridin-4-yl)-methyl]carbamoylmethyl]-2-trifluoromethylimidazo[1,2-a]-pyridine hydrochloride

mp : 175-200°C

NMR (DMSO-d_6, δ) : 4.29 (2H, s), 4.59 (2H, d, J=6Hz), 7.14 (1H, t, J=8Hz), 7.45-7.58 (3H, m), 7.92 (2H, d, J=8Hz), 8.27 (2H, d, J=8Hz), 8.39 (2H, d, J=8Hz), 8.89 (2H, d, J=8Hz), 9.19 (1H, s)

Example 210

8-(2,6-Dichlorobenzoylamino)-3-[[N-methyl-N-(pyridin-2-yl)methyl]carbamoylmethyl]-2-trifluoromethylimidazo[1,2-a]-pyridine hydrochloride

mp : 218-225°C

NMR (DMSO-d_6, δ) : 2.88 (6/5H, s), 3.32 (9/5H, s), 4.48 (2H, s), 4.78 (6/5H, s), 4.92 (4/5H, s), 7.07-7.21 (1H, m), 7.45-7.57 (3H, m), 7.63-7.70 (1H, m), 7.97 (1H, t, J=8Hz), 8.19-8.30 (2H, m), 8.34 (1H, d, J=8Hz), 8.73 (1H, d, J=8Hz)

Example 211

8-(2,6-Dichlorobenzoylamino)-3-(morpholinocarbonylmethyl)-2-trifluoromethylimidazo[1,2-a]pyridine

mp : 256-257°C

NMR ($CDCl_3$, δ) : 3.60-3.75 (8H, m), 4.13 (2H, s), 7.00 (1H, t, J=8Hz), 7.32-7.43 (3H, m), 8.02 (1H, d, J=8Hz), 8.52 (1H, d, J=8Hz), 8.71 (1H, s)

ESI-MASS : 501 (M^++1)

Example 212

3-(N-Carbamoylmethyl-N-methylaminomethyl)-8-(2,6-dichlorobenzoylamino)-2-trifluoromethylimidazo[1,2-a]pyridine

mp : 219-222°C

NMR ($CDCl_3$, δ) : 2.38 (3H, s), 3.14 (2H, s), 4.05 (2H, s), 5.45 (1H, s), 6.40 (1H, s), 7.07 (1H, t, J=8Hz), 7.30-7.44 (3H, m), 8.12 (1H, d, J=8Hz), 8.56 (1H, d, J=8Hz), 8.81 (1H, s)

Example 213

A mixture of 8-(2,6-dichlorobenzoylamino)-3-[N-(2-aminopyridin-3-yl)carbamoylmethyl]-2-trifluoromethylimidazo-[1,2-a]pyridine (60 mg) and methanesulfonic acid (12 mg) was dissolved in ethanol (1.2 ml) at 60°C. The resulting solution was concentrated in vacuo and the obtained oil was crystallized from diethyl ether to give 8-(2,6-dichlorobenzoylamino)-3-[N-(2-aminopyridin-3-yl)carbamoylmethyl]-2-trifluoromethylimidazo[1,2-a]pyridine methanesulfonate (59 mg).

mp : 252-253°C

NMR (DMSO-d_6, δ) : 2.34 (3H, s), 4.40 (2H, s), 6.90 (1H, t, J=8Hz), 7.16 (1H, t, J=8Hz), 7.46-7.56 (3H, m), 7.82-7.92 (3H, m), 8.02 (1H, d, J=8Hz), 8.28 (1H, d, J=8Hz), 8.40 (1H, d, J=8Hz), 10.04 (1H, s), 11.26 (1H, s)

The following compound was obtained according to a

similar manner to that of Example 213.

Example 214

8-(2,6-Dichlorobenzoylamino)-3-(imidazo[5,4-b]pyridin-2-yl)methyl-2-trifluoromethylimidazo[1,2-a]pyridine methanesulfonate

mp : 205-212°C

NMR (DMSO-d_6, δ) : 5.01 (2H, s), 7.15 (1H, t, J=8Hz), 7.45-7.58 (4H, m), 8.25-8.33 (2H, m), 8.38 (1H, d, J=8Hz), 8.50 (1H, d, J=6Hz)

The following compound was obtained according to a similar manner to that of Example 7.

Example 215

3-(N-Carboxymethyl-N-methylaminomethyl)-8-(2,6-dichlorobenzoylamino)-2-trifluoromethylimidazo[1,2-a]pyridine

NMR (DMSO-d_6, δ) : 2.21 (3H, s), 3.32 (2H, s), 4.12 (2H, s), 7.15 (1H, t, J=8Hz), 7.45-7.57 (3H, m), 8.29 (1H, d, J=8Hz), 8.69 (1H, d, J=8Hz)

ESI-MASS : 473 (M^++1)

The following compounds [Examples 216 to 226] were obtained according to a similar manner to that of Example 100.

Example 216

3-(N-Cyanomethyl-N-methylaminomethyl)-8-(2,6-dichlorobenzoylamino)-2-trifluoromethylimidazo[1,2-a]pyridine

mp : 206-210°C

NMR ($CDCl_3$, δ) : 2.47 (3H, s), 3.50 (2H, s), 4.08 (2H, s), 7.05 (1H, t, J=8Hz), 7.32-7.45 (3H, m), 8.02 (1H, d, J=8Hz), 8.57 (1H, d, J=8Hz), 8.73 (1H, s)

ESI-MASS : 456 (M^++1)

Example 217

8-(2,6-Dichlorobenzoylamino)-3-[[N-(2-hydroxyethyl)-N-methyl]aminomethyl]-2-trifluoromethylimidazo[1,2-a]pyridine

mp : 214-218 °C

NMR ($CDCl_3$, δ) : 2.13 (1H, br), 2.28 (3H, s), 2.67 (2H, t, J=6Hz), 3.70 (2H, q, J=6Hz), 4.02 (2H, s), 7.02 (1H, t, J=8Hz), 7.29-7.45 (3H, m), 8.13 (1H, d, J=8Hz), 8.55 (1H, d, J=8Hz), 8.80 (1H, s)

ESI-MASS : 461 (M^++1)

Example 218

8-(2,6-Dichlorobenzoylamino)-3-(4-ethoxycarbonyl-piperazin-1-yl)methyl-2-trifluoromethylimidazo[1,2-a]pyridine

mp : 213-216°C

NMR ($CDCl_3$, δ) : 1.25 (3H, t, J=6Hz), 2.46 (4H, br s), 3.47 (4H, br s), 3.95 (2H, s), 4.14 (2H, q, J=6Hz), 7.01 (1H, t, J=8Hz), 7.32-7.44 (3H, m), 8.16 (1H, d, J=8Hz), 8.55 (1H, d, J=8Hz), 8.74 (1H, s)

Example 219

8-(2,6-Dichlorobenzoylamino)-3-[[N-(2-hydroxyethyl)-N-methylamino]methyl]-2-trifluoromethylimidazo[1,2-a]pyridine hydrochloride

mp : 238-240°C

NMR (DMSO-d_6, δ) : 2.79 (3H, br), 3.43 (4H, br), 3.35 (2H, br), 7.29 (1H, t, J=8Hz), 7.47-7.60 (3H, m), 8.39 (1H, d, J=8Hz), 8.65 (1H, d, J=8Hz)

ESI-MASS : 461 (M^++1)

Example 220

8-(2,6-Dichlorobenzoylamino)-3-[[N-[2-(N',N'-dimethylamino)ethyl]-N-methylamino]methyl]-2-trifluoromethylimidazo[1,2-a]pyridine dihydrochloride

mp : 168-175°C

NMR (DMSO-d_6, δ) : 3.33-4.00 (15H, br), 7.70 (1H, t,

J=8Hz), 7.58-7.95 (3H, m), 8.35 (1H, d, J=8Hz), 8.50-8.70 (1H, br)

Example 221

8-(2,6-Dichlorobenzoylamino)-3-[[N-(pyridin-2-yl)methyl-N-methylamino]methyl]-2-trifluoromethylimidazo[1,2-a]pyridine dihydrochloride

mp : 169-174°C

NMR (DMSO-d_6, δ) : 2.70 (3H, s), 4.62 (2H, s), 4.82 (2H, s), 7.30 (1H, t, J=8Hz), 7.45-7.67 (6H, m), 8.05 (1H, t, J=8Hz), 8.66-8.75(2H, m), 8.88 (1H, d, J=8Hz)

ESI-MASS : 508 (M^++1)

Example 222

3-[N,N-bis(2-Hydroxyethyl)aminomethyl]-8-(2,6-dichlorobenzoylamino)-2-trifluoromethylimidazo[1,2-a]pyridine hydrochloride

mp : 195-198°C

NMR (DMSO-d_6, δ) : 3.10-3.70 (4H, br), 3.82 (4H, br), 5.01 (2H, br), 7.30 (1H, t, J=8Hz), 7.47-7.60 (3H, m), 8.40 (1H, d, J=8Hz), 8.64 (1H, d, J=8Hz)

ESI-MASS : 491 (M^++1)

Example 223

8-(2,6-Dichlorobenzoylamino)-3-(4-hydroxypiperidin-1-yl)methyl-2-trifluoromethylimidazo[1,2-a]pyridine hydrochloride

mp : 198-205°C

NMR (DMSO-d_6, δ) : 1.60-2.05 (3H, m), 3.05-3.70 (6H, m), 4.75-4.92 (2H, m), 7.28 (1H, t, J=8Hz), 7.47-7.58 (3H, m), 8.39 (2H, d, J=8Hz), 8.78 (1H, t, J=8Hz)

ESI-MASS : 487 (M^++1)

Example 224

3-(4-Acetylpiperazin-1-yl)methyl-8-(2,6-dichlorobenzoylamino)-2-trifluoromethylimidazo[1,2-a]pyridine hydrochloride

mp : 230-232°C

NMR (DMSO-d_6, δ) : 2.02 (3H, s), 3.40-3.75 (10H, br), 7.25 (1H, t, J=8Hz), 7.45-7.58 (3H, m), 8.37 (1H, d, J=8Hz), 8.67 (1H, br)

ESI-MASS : 514 (M^++1)

Example 225

8-(2,6-Dichlorobenzoylamino)-3-[2-(imidazol-1-yl)ethyl]-2-methylimidazo[1,2-a]pyridine

mp : >250°C

NMR (DMSO-d_6, δ) : 2.03 (3H, s), 3.33 (2H, t, J=6Hz), 4.18 (2H, t, J=6Hz), 6.83 (1H, s), 6.88 (1H, t, J=7Hz), 7.10 (1H, s), 7.41 (1H, s), 7.42-7.53 (3H, m), 8.05 (1H, d, J=7Hz), 8.12 (1H, d, J=7Hz)

Example 226

8-(2,6-Dichlorobenzoylamino)-3-[2-(imidazol-1-yl)ethyl]-2-trifluoromethylimidazo[1,2-a]pyridine

mp : 252-254°C

NMR (DMSO-d_6, δ) : 3.54 (2H, t, J=6Hz), 4.26 (2H, t, J=6Hz), 6.81 (1H, s), 7.05-7.12 (2H, m), 7.43-7.57 (4H, m), 8.21-8.28 (2H, m)

Example 227

A mixture of 8-(2,6-dichlorobenzoylamino)-3-formyl-2-trifluoromethylimidazo[1,2-a]pyridine (200 mg) and 2-aminoethanol (33 mg) in ethanol (4 ml) was refluxed for 10 hours. The reaction mixture was cooled to ambient temperature and the precipitate was filtered and washed with ethanol (3 ml) to give (EZ)-8-(2,6-dichlorobenzoylamino)-3-[N-(2-hydroxyethyl)iminomethyl]-2-trifluoromethylimidazo-[1,2-a]pyridine (198 mg).

mp : 236-238°C

NMR ($CDCl_3$, δ) : 2.00 (1H, t, J=6Hz), 3.85 (2H, t, J=6Hz), 3.92-4.00 (2H, m), 7.13 (1H, t, J=8Hz), 7.33-7.43 (3H, m), 8.68 (1H, d, J=8Hz), 8.71 (1H, s), 8.92 (1H, s), 9.55 (1H, d, J=8Hz)

Example 228

A mixture of (EZ)-8-(2,6-dichlorobenzoylamino)-3-[N-(2-hydroxyethyl)iminomethyl]-2-trifluoromethylimidazo[1,2-a]-pyridine (180 mg) and sodium cyanoborohydride in dichloromethane (2 ml) and methanol (1 ml) was stirred overnight at ambient temperature. The reaction mixture was evaporated under reduced pressure. The residue was diluted with dichloromethane (10 ml) and washed with water (5 ml). The organic layer was dried over sodium sulfate and evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel with 1% methanol in dichloromethane (V/V) as an eluent. The obtained product was treated with hydrogen chloride in ethanol (7N, 1 ml). The precipitate was filtered and washed with ethanol to give 8-(2,6-dichlorobenzoylamino)-3-[N-(2-hydroxyethyl)-aminomethyl]-2-trifluromethylimidazo[1,2-a]pyridine hydrochloride (75 mg).

mp : 244-246°C

NMR (DMSO-d_6, δ) : 3.14 (2H, br t, J=6Hz), 3.73 (2H, br), 4.75 (2H, s), 5.32 (1H, br), 7.27 (1H, t, J=8Hz), 7.46-7.58 (3H, m), 8.36 (1H, d, J=8Hz), 8.66 (1H, d, J=8Hz), 9.26 (1H, br)

The following compound was obtained according to a similar manner to that of Examples 227 and 228.

Example 229

8-(2,6-Dichlorobenzoylamino)-3-[N-(2-hydroxyethyl)-aminomethyl]-2-trifluoromethylimidazo[1,2-a]pyridine

mp : 213-215°C

NMR ($CDCl_3$, δ) : 2.82 (2H, t, J=5Hz), 3.69 (2H, t, J=5Hz), 4.28 (2H, s), 7.01 (1H, t, J=8Hz), 7.32-7.43 (3H, m), 8.15 (1H, d, J=8Hz), 8.53 (1H, d, J=8Hz), 8.78 (1H, s)

Example 230

To a mixture of 8-(2,6-dichlorobenzoylamino)-3-[[N-(2-hydroxyethyl)-N-methylamino]methyl]-2-trifluoromethylimidazo-[1,2-a]pyridine (140 mg) and carbon tetrabromide (121 mg) in dichloromethane (5 ml) was added triphenylphosphine (119 mg) portionwise and the mixture was stirred for 30 minutes at ambient temperature. The reaction mixture was evaporated under reduced pressure and the residue was purified by flash column chromatography on silica gel with 20% ethyl acetate in n-hexane (V/V) as an eluent. The fractions containing product were evaporated under reduced pressure. The residue was crystallized spontaneously and the crystal was triturated with diisopropyl ether to give 3-[[N-(2-bromoethyl)-N-methyl]aminomethyl]-8-(2,6-dichlorobenzoylamino)-2-trifluoromethylimidazo[1,2-a]pyridine (144 mg).

mp : 182-184°C

NMR ($CDCl_3$, δ) : 2.25 (3H, s), 2.90 (2H, t, J=6Hz), 3.47 (2H, t, J=6Hz), 4.00 (2H, s), 7.00 (1H, t, J=8Hz), 7.30-7.45 (3H, m), 8.36 (1H, d, J=8Hz), 8.54 (1H, d, J=8Hz), 8.70 (1H, s)

The following compound was obtained according to a similar manner to that of Example 230.

Example 231

3-(2-Bromoethyl)-8-(2,6-dichlorobenzoylamino)-2-trifluoromethylimidazo[1,2-a]pyridine

mp : 170-171°C

NMR ($CDCl_3$, δ) : 3.52-3.70 (4H, m), 7.04 (1H, t,

J=7Hz), 7.30-7.43 (3H, m), 7.90 (1H, d, J=7Hz), 8.52 (1H, d, J=7Hz), 8.71 (1H, br s)

Example 232

A mixture of 3-[[N-(2-bromoethyl)-N-methyl]aminomethyl]-8-(2,6-dichlorobenzoylamino)-2-trifluoromethylimidazo[1,2-a]-pyridine (100 mg), 2-mercaptoimidazole (23 mg), potassium carbonate (53 mg) and potassium iodide (63 mg) in N,N-dimethylformamide (1 ml) was stirred for 1.5 hours at ambient temperature. The reaction mixture was partitioned between ethyl acetate and water and the organic layer was washed with water. The organic layer was dried over sodium sulfate and evaporated under reduced pressure. The residue was treated with hydrogen chloride in ethanol (7N, 1 ml) and evaporated. The residue was crystallized spontaneously and triturated with ethyl acetate to give 8-(2,6-dichlorobenzoylamino)-3-[[N-[2-(imidazol-2-yl)thioethyl]-N-methylamino]methyl]-2-trifluoromethylimidazo[1,2-a]pyridine dihydrochloride (91 mg).

mp : 231-233°C

NMR (DMSO-d_6, δ) : 2.65 (3H, s), 3.39 (2H, br), 3.74 (2H, br), 4.70 (2H, br), 7.25 (1H, t, J=8Hz), 7.47-7.57 (3H, m), 7.72 (2H, s), 8.38 (1H, d, J=8Hz), 8.65 (1H, d, J=8Hz)

The following compounds [Examples 233 to 238] were obtained according to a similar manner to that of Example 232.

Example 233

8-(2,6-Dichlorobenzoylamino)-3-(pyridin-2-yl)thiomethyl-2-trifluoromethylimidazo[1,2-a]pyridine hydrochloride

mp : 186-188°C

NMR (DMSO-d_6, δ) : 5.02 (2H, s), 7.16-7.23 (2H, m), 7.35 (1H, d, J=8Hz), 7.45-7.57 (3H, m), 7.65-7.72

(1H, m), 8.30 (1H, d, J=8Hz), 8.47 (1H, d, J=8Hz), 8.51 (1H, dd, J=6 and 2Hz)

ESI-MASS : 497 (M^++1)

Example 234

8-(2,6-Dichlorobenzoylamino)-3-(pyridin-4-yl)thiomethyl-2-trifluoromethylimidazo[1,2-a]pyridine hydrochloride

mp : >210°C

NMR (DMSO-d_6, δ) : 5.18 (1H, s), 7.27 (1H, t, J=8Hz), 7.46-7.58 (3H, m), 7.90-7.96 (2H, m), 8.36 (1H, d, J=8Hz), 8.55 (1H, d, J=8Hz), 8.70 (2H, d, J=6Hz)

ESI-MASS : 497 (M^++1)

Example 235

3-(Benzimidazol-2-yl)thiomethyl-8-(2,6-dichlorobenzoylamino)-2-trifluoromethylimidazo[1,2-a]pyridine hydrochloride

mp : >250°C

NMR (DMSO-d_6, δ) : 5.13 (2H, s), 7.24 (1H, t, J=8Hz), 7.33 (2H, m), 7.42-7.56 (3H, m), 7.61 (2H, m), 8.32 (1H, d, J=8Hz), 8.61 (1H, d, J=8Hz)

Example 236

8-(2,6-Dichlorobenzoylamino)-3-(imidazo[5,4-b]pyridin-2-yl)thiomethyl-2-trifluoromethylimidazo[1,2-a]pyridine hydrochloride

mp : >250°C

NMR (DMSO-d_6, δ) : 5.22 (2H, s), 7.25 (1H, t, J=8Hz), 7.37-7.57 (4H, m), 8.18 (1H, d, J=8Hz), 8.33 (1H, d, J=8Hz), 8.41 (1H, d, J=5Hz), 8.60 (1H, d, J=8Hz)

ESI-MASS : 537 (M^++1)

Example 237

8-(2,6-Dichlorobenzoylamino)-3-(imidazol-2-yl)thio-2-trifluoromethylimidazo[1,2-a]pyridine

mp : 147-151°C

NMR (DMSO-d_6, δ) : 6.90 (1H, br), 7.15 (1H, br), 7.30 (1H, d, J=8Hz), 7.45-7.58 (3H, m), 8.40 (1H, d, J=8Hz), 8.52 (1H, d, J=8Hz)

Example 238

8-(2,6-Dichlorobenzoylamino)-3-[2-(imidazol-2-yl)thioethyl]-2-trifluoromethylimidazo[1,2-a]pyridine

mp : 123-127°C

NMR (DMSO-d_6, δ) : 3.24 (2H, t, J=7Hz), 3.48 (2H, t, J=7Hz), 7.02 (1H, br s), 7.13 (1H, t, J=7Hz), 7.20 (1H, br s), 7.43-7.58 (3H, m), 8.26 (1H, d, J=7Hz), 8.56 (1H, d, J=7Hz)

Example 239

To a solution of sodium sulfide (136 mg) in N,N-dimethylformamide (2 ml) was added 3-chloromethyl-8-(2,6-dichlorobenzoylamino)-2-trifluoromethylimidazo[1,2-a]pyridine (200 mg) portionwise and the mixture was stirred for 2 hours at ambient temperature. The reaction mixture was poured into ice-water and extracted with ethyl acetate. The extract was washed with water, dried over sodium sulfate and evaporated under reduced pressure. The residue was crystallized spontaneously and the crystal was triturated with diisopropyl ether to give 8-(2,6-dichlorobenzoylamino)-3-mercaptomethyl-2-trifluoromethylimidazo[1,2-a]pyridine (186 mg).

mp : 163-173°C

NMR ($CDCl_3$, δ) : 4.23 (2H, s), 7.01 (1H, t, J=8Hz), 7.30-7.46 (3H, m), 7.65 (1H, d, J=8Hz), 8.57 (1H, d, J=8Hz), 8.75 (1H, s)

Example 240

A mixture of 3-chloromethyl-8-(2,6-dichlorobenzoylamino)-2-trifluoromethylimidazo[1,2-a]pyridine (127 mg) and thiourea (29.7 mg) in ethanol (2 ml) was stirred at ambient temperature for 2 hours. The mixture was evaporated in vacuo

and the residue was crystallized from ethyl acetate to give 3-(amidinothiomethyl)-8-(2,6-dichlorobenzoylamino)-2-trifluoromethylimidazo[1,2-a]pyridine hydrochloride (116 mg).

mp : 215-218°C

NMR (DMSO-d_6, δ) : 5.17 (1H, s), 7.29 (1H, t, J=8Hz), 7.45-7.60 (3H, m), 8.36 (1H, d, J=8Hz), 8.62 (1H, d, J=8Hz), 9.45 (4H, m)

The following compounds [Examples 241 to 245] were obtained according to a similar manner to that of Example 12.

Example 241

8-(2,6-Dichlorobenzoylamino)-3-(imidazol-2-yl)thio-2-trifluoromethylimidazo[1,2-a]pyridine hydrochloride

mp : >250°C

NMR (DMSO-d_6, δ) : 7.35 (1H, t, J=8Hz), 7.45-7.60 (5H, m), 8.49 (1H, d, J=8Hz), 8.58 (1H, d, J=8Hz)

Example 242

8-(2,6-Dichlorobenzoylamino)-3-[2-(imidazol-2-yl)thioethyl]-2-trifluoromethylimidazo[1,2-a]pyridine hydrochloride

mp : 160-170°C

NMR (DMSO-d_6, δ) : 3.46 (2H, t, J=7Hz), 3.61 (2H, t, J=7Hz), 7.18 (1H, t, J=7Hz), 7.44-7.58 (3H, m), 7.72 (2H, s), 8.28 (1H, d, J=7Hz), 8.42 (1H, d, J=7Hz)

Example 243

8-(2,6-Dichlorobenzoylamino)-3-[2-(imidazol-1-yl)ethyl]-2-methylimidazo[1,2-a]pyridine dihydrochloride

mp : >250°C

NMR (DMSO-d_6, δ) : 2.09 (3H, s), 3.58 (2H, t, J=6Hz), 4.45 (2H, t, J=6Hz), 7.45-7.62 (5H, m), 7.69 (1H, s), 7.85 (1H, s), 8.65-8.80 (2H, m), 9.08 (1H, s)

Example 244

8-(2,6-Dichlorobenzoylamino)-3-[2-(imidazol-1-yl)ethyl]-2-trifluoromethylimidazo[1,2-a]pyridine hydrochloride

mp : >250°C

NMR (DMSO-d_6, δ) : 3.68 (2H, t, J=6Hz), 4.49 (2H, t, J=6Hz), 7.20 (1H, t, J=7Hz), 7.43-7.58 (3H, m), 7.67 (1H, s), 7.78 (1H, s), 8.33 (1H, d, J=7Hz), 8.51 (1H, d, J=7Hz), 9.05 (1H, s)

Example 245

8-(2,6-Dichlorobenzoylamino)-3-(2-hydroxy-2-methylpropyl)-2-methylimidazo[1,2-a]pyridine hydrochloride

mp : >250°C

NMR (DMSO-d_6, δ) : 1.20 (6H, s), 2.47 (3H, s), 3.10 (2H, s), 7.42 (1H, t, J=7Hz), 7.50-7.65 (3H, m), 8.59 (1H, d, J=7Hz), 8.71 (1H, d, J=7Hz)

Example 246

To a solution of 8-(2,6-dichlorobenzoylamino)-3-(imidazol-2-yl)thio-2-trifluoromethylimidazo[1,2-a]pyridine (118 mg) in dichloromethane (2 ml) was added m-chloroperbenzoic acid and the mixture was stirred at ambient temperature for 2 hours. The resulting mixture was purified by column chromatography on silica gel and the less polar fractions were combined and evaporated in vacuo. The obtained oil was crystallized from diethyl ether to give 8-(2,6-dichlorobenzoylamino)-3-(imidazol-2-yl)sulfonyl-2-trifluoromethylimidazo[1,2-a]pyridine (8.5 mg).

mp : >250°C

NMR (DMSO-d_6, δ) : 7.39 (2H, br), 7.45-7.60 (4H, m), 8.52 (1H, d, J=8Hz), 8.96 (1H, d, J=8Hz)

The more polar fraction was combined and concentrated in vacuo. The residual oil was crystallized from diethyl ether to give 8-(2,6-dichlorobenzoylamino)-3-(imidazol-2-

yl)sulfinyl-2-trifluoromethylimidazo[1,2-a]pyridine (75 mg).

mp : 236-239°C

NMR (DMSO-d_6, δ) : 7.25-7.40 (3H, m), 7.45-7.60 (3H, m), 8.47 (1H, d, J=8Hz), 8.62 (1H, d, J=8Hz)

Example 247

To a suspension of sodium borohydride (26 mg) in tetrahydrofuran (1.5 ml) at 0°C was added boron trifluoride diethyl etherate (0.11 ml) and stirred for 30 minutes at the same temperature. To the mixture was added 3-carboxymethyl-8-(2,6-dichlorobenzoylamino)-2-trifluoromethylimidazo-[1,2-a]pyridine (150 mg) and the mixture was stirred for 30 minutes at the same temperature and 2 days at ambient temperature. To the mixture was added methanol (0.5 ml) and 1N-hydrochloric acid (2 ml) and the mixture was stirred for 1 hour at 60°C. The mixture was extracted with ethyl acetate and the extract was dried over sodium sulfate and evaporated under reduced pressure. The residue was crystallized from diisopropyl ether to give 8-(2,6-dichlorobenzoylamino)-3-(2-hydroxyethyl)-8-(2,6-dichlorobenzoylamino)-2-trifluoromethylimidazo[1,2-a]pyridine (113 mg).

mp : 174-176°C

NMR ($CDCl_3$, δ) : 1.88 (1H, t, J=5Hz), 3.31 (2H, t, J=5Hz), 3.95 (2H, q, J=5Hz), 6.99 (1H, t, J=8Hz), 7.30-7.43 (3H, m), 8.01 (1H, d, J=8Hz), 8.49 (1H, d, J=8Hz), 8.83 (1H, s)

The following compound was obtained according to a similar manner to that of Example 247.

Example 248

8-(2,6-Dichlorobenzoylamino)-3-(2-hydroxyethyl)-2-methylimidazo[1,2-a]pyridine

mp : 214-216°C

NMR (DMSO-d_6, δ) : 3.04 (2H, t, J=6Hz), 3.60 (2H, q,

J=6Hz), 4.75 (1H, ,t, J=6Hz), 6.87 (1H, t, J=7Hz), 7.40-7.55 (3H, m), 8.01 (1H, d, J=7Hz), 8.12 (1H, d, J=8Hz)

Example 249

To a solution of sodium ethoxide (36 mg) in ethanol (2 ml) was added ethyl acetoacetate (69 mg) and then 3-chloromethyl-8-(2,6-dichlorobenzoylamino)-2-trifluoromethylimidazo[1,2-a]pyridine (150 mg) and the mixture was stirred for 3 hours at 50°C. The pH of mixture was adjusted to 3-4 with 1N-hydrochloric acid and the mixture was extracted with ethyl acetate. The extract was evaporated under reduced pressure. The residue and hydrazine monohydrate (34 mg) was dissolved in isopropanol (1 ml) and the mixture was refluxed overnight. The mixture was evaporated under reduced pressure and the residue was crystallized from diethyl ether to give 8-(2,6-dichlorobenzoylamino)-3-(5-hydroxy-3-methylpyrazol-4-yl)methyl-2-trifluoromethylimidazo[1,2-a]pyridine (75 mg).

mp : >250°C

NMR (DMSO-d_6, δ) : 1.91 (3H, s), 2.09 (1H, s), 4.05 (2H, s), 7.09 (1H, t, J=8Hz), 7.45-7.55 (3H, m), 8.15-8.25 (2H, m)

Example 250

To a suspension of 3-carboxymethyl-8-(2,6-dichlorobenzoylamino)-2-trifluoromethylimidazo[1,2-a]pyridine (200 mg) in dichloromethane (2 ml) was added oxalyl chloride (81 µl) and N,N-dimethylformamide (1 drop). The mixture was stirred for 1 hour at ambient temperature and then evaporated under reduced pressure. The residue was dissolved in dichloromethane (2 ml). To the solution was added acetylhydrazine and the mixture was stirred for 2 hours at ambient temperature. The precipitate was filtered and washed with water. The obtained solid was suspended in phosphorus-

oxychloride (1.5 ml) and refluxed for 5 hours. The reaction mixture was evaporated under reduced pressure. The residue was poured into ice-water and neutralized with aqueous sodium hydrogen carbonate. The aqueous suspension was extracted with ethyl acetate and extract was dried over sodium sulfate and evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel with ethyl acetate as eluent. The fractions containing product were evaporated under reduced pressure. The residue was crystallized from isopropyl ether to give 8-(2,6-dichlorobenzoylamino)-3-(2-methyl-1,3,4-oxadiazol-5-yl)methyl-2-trifluoromethylimidazo[1,2-a]pyridine (83 mg).

mp : 210-213°C

NMR ($CDCl_3$, δ) : 2.49 (3H, s), 4.66 (2H, s), 7.05 (1H, t, J=8Hz), 7.32-7.43 (3H, m), 8.02 (1H, d, J=8Hz), 8.55 (1H, d, J=8Hz), 8.69 (1H, s)

Example 251

A solution of 8-(2,6-dichlorobenzoylamino)-3-[N-(2-aminopyridin-3-yl)carbamoylmethyl]-2-trifluoromethylimidazo-[1,2-a]pyridine (100 mg) in acetic acid (1 ml) was refluxed overnight. The mixture was evaporated under reduced pressure. The residue was crystallized from dichloromethane to give 8-(2,6-dichlorobenzoylamino)-3-(imidazo[5,4-b]-pyridine-2-yl)methyl-2-trifluoromethylimidazo[1,2-a]pyridine (72 mg).

mp : >250°C

NMR (DMSO-d_6, δ) : 4.85 (2H, s), 7.10-7.20 (2H, m), 7.47-7.58 (3H, m), 7.87 (1H, d, J=8Hz), 8.23-8.38 (3H, m), 11.30 (1H, s)

Example 252

To a stirred mixture of 8-(2,6-dichlorobenzoylamino)-3-(2-hydroxyethyl)-2-methylimidazo[1,2-a]pyridine (1.00 g) and N-bromosuccinimide (588 mg) in dichloromethane (20 ml) was

added triphenylphosphine (792 mg) in dichloromethane (2 ml) dropwise in an ice bath and the resulting mixture was stirred at ambient temperature for 1 hour. The mixture was purified by column chromatography on silica gel and the obtained oil was crystallized from diethyl ether to give 3-(2-bromoethyl)-8-(2,6-dichlorobenzoylamino)-2-methylimidazo[1,2-a]pyridine (640 mg).

mp : 208-210°C

NMR ($CDCl_3$, δ) : 3.40-3.60 (4H, m), 6.88 (1H, t, J=7Hz), 7.28-7.42 (3H, m), 7.72 (1H, d, J=7Hz), 8.35 (1H, d, J=7Hz), 8.71 (1H, br s)

Example 253

Thionyl chloride (377 mg) was added to methanol (10 ml) dropwise at -70°C and to the mixture was added 3-carboxymethyl-8-(2,6-dichlorobenzoylamino)-2-methylimidazo[1,2-a]pyridine (400 mg). The mixture was stirred for 10 minutes and allowed to warm to ambient temperature gradually. Then, the mixture was refluxed for 2 hours, allowed to cool to ambient temperature and partitioned between dichloromethane and aqueous saturated sodium bicarbonate. The organic layer was separated, washed with brine, dried and evaporated in vacuo. The crystalline residue was triturated with diisopropyl ether to give 8-(2,6-dichlorobenzoylamino)-3-methoxycarbonylmethyl-2-methylimidazo[1,2-a]pyridine (360 mg).

mp : 172-173°C

NMR (DMSO-d_6, δ) : 2.31 (3H, s), 3.63 (3H, s), 4.12 (2H, s), 6.90 (1H, t, J=7Hz), 7.41-7.55 (3H, m), 8.02-8.10 (2H, m)

The following compound was obtained according to a similar manner to that of Example 253.

Example 254

8-(2,6-Dichlorobenzoylamino)-3-methoxycarbonylmethyl-2-trifluoromethylimidazo[1,2-a]pyridine

mp : 168-169°C

NMR ($CDCl_3$, δ) : 3.72 (3H, s), 4.09 (2H, s), 7.03 (1H, t, J=7Hz), 7.30-7.43 (3H, m), 7.82 (1H, d, J=7Hz), 8.53 (1H, d, J=7Hz), 8.70 (1H, br s)

The following compounds [Examples 255 to 256] were obtained according to a similar manner to that of Preparation 22.

Example 255

8-(2,6-Dichlorobenzoylamino)-3-(2-hydroxy-2-methylpropyl)-2-methylimidazo[1,2-a]pyridine

mp : 245-246°C

NMR (DMSO-d_6, δ) : 1.14 (6H, s), 2.31 (3H, s), 2.95 (2H, s), 4.48 (1H, s), 6.80 (1H, t, J=7Hz), 7.42-7.57 (3H, m), 8.00 (1H, d, J=7Hz), 8.23 (1H, d, J=7Hz)

Example 256

8-(2,6-Dichlorobenzoylamino)-3-(2-hydroxy-2-methylpropyl)-2-trifluoromethylimidazo[1,2-a]pyridine

mp : 213-215°C

NMR ($CDCl_3$, δ) : 1.35 (6H, s), 1.42 (1H, s), 3.21 (2H, s), 6.91 (1H, t, J=7Hz), 7.30-7.42 (3H, m), 8.22 (1H, d, J=7Hz), 8.46 (1H, d, J=7Hz), 8.75 (1H, s)

Example 257

A solution of 3-chloromethyl-8-(2,6-dichlorobenzoylamino)-2-trifluoromethylimidazo[1,2-a]pyridine (200 mg) in triethylphosphite (0.5 ml) was stirred for 7 hours at 100°C. The reaction mixture was diluted with toluene (3 ml) and evaporated under reduced pressure. The residue was crystallized spontaneously and the crystal was

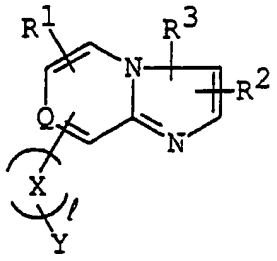
triturated with diethyl ether to give 8-(2,6-dichlorobenzoylamino)-3-diethoxyphosphorylmethyl-2-trifluoromethylimidazo[1,2-a]pyridine (110 mg).

mp : 193-196°C

NMR ($CDCl_3$, δ) : 1.28 (6H, t, J=6Hz), 3.61 (2H, d, J=20Hz), 4.69 (4H, quint., J=6Hz), 7.04 (1H, t, J=8Hz), 7.32-7.43 (3H, m), 8.05 (1H, d, J=8Hz), 8.53 (1H, d, J=8Hz), 8.72 (1H, s)

C L A I M S

1. A compound of the formula :



wherein

R^1 is hydrogen, lower alkyl, an acyl group, amino, acylamino, nitro, halogen or hydroxy(lower)alkyl which may have one or more suitable substituent(s),

R^2 is hydrogen, lower alkyl, an acyl group, lower alkoxy, acyl(lower)alkyl, aryl, cyano, mono-(or di- or tri-)-halo(lower)alkyl, lower alkylthio or hydroxy(lower)alkyl which may have one or more suitable substituent(s),

R^3 is hydrogen, lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy, cyclo(lower)alkyl(lower)alkyl, halogen, an acyl group, acyl(lower)alkyl, acylamino, acylamino(lower)alkyl, acyl(lower)alkenyl, acyloxy(lower)alkyl, acyl(lower)alkylthio(lower)alkyl, amino(lower)alkyl, mono-(or di-)lower alkylamino, lower alkylthio(lower)alkyl, hydroxyimino(lower)alkyl which may have one or more suitable substituent(s), hydroxy(lower)alkyl which may have one or more suitable substituent(s), hydroxy(lower)alkylthio(lower)alkyl, cyano(lower)alkyl, mono-(or di-)lower alkoxy(lower)alkyl which may have one or more suitable substituent(s), lower alkyl substituted with aryl which may have one or

more suitable substituent(s), mono-(or di-)lower alkylamino(lower)alkyl, tri(lower)alkylammonio(lower)-alkyl, lower alkyl substituted with heterocyclic group which may have one or more suitable substituent(s), hydrazino(lower)alkyl which may have one or more suitable substituent(s), mono- or di-(lower)alkoxy(lower)alkylamino(lower)alkyl, (lower)alkylamino(lower)alkyl which may have one or more suitable substituent(s), heterocyclic group which may have one or more suitable substituent(s), heterocyclicthio, heterocyclicthio(lower)alkyl which may have one or more suitable substituent(s), heterocyclicoxy, heterocyclicoxy(lower)alkyl, heterocyclicaminoimino(lower)alkyl, aryl which may have one or more suitable substituent(s), amino, nitro, halo(lower)alkyl, hydroxy(lower)alkylimino(lower)alkyl, hydroxy(lower)alkylamino(lower)alkyl, bis-[hydroxy(lower)alkyl]amino(lower)alkyl, mercapto(lower)alkyl or amidinothio(lower)alkyl,

in which R^2 and R^3 may be linked together to form

(1) lower alkylene which may have one or more suitable substituent(s),

(2) lower alkenylene which may have one or more suitable substituent(s), or

(3) a group of the formula :

$$-(A^1)_m-W-(A^2)_n-$$

[wherein A^1 and A^2 are each lower alkylene which may have one or more suitable substituent(s) or lower alkenylene which may have one or more suitable substituent(s),

W is -S-, $-\overset{\overset{O}{\|}}{S}-$, or $-\overset{\overset{R^4}{|}}{N}-$ (wherein R^4 is hydrogen, lower alkyl or an acyl group) and

m and n are each an integer of 0 or 1],

X is vinylene, or a group of the formula :

$-NHCO-$, $-NHSO_2-$, $-OCO-$, $-OCH_2-$, $-NHCOCO-$, $-NHCOCH=CH-$, $-NHCOCH_2-$, $-NHCONH-$ or $-\overset{\overset{R^5}{|}}{N}-CO-$

(wherein R^5 is lower alkyl),

Y is heterocyclic group which may have one or more suitable substituent(s), or aryl which may have one or more suitable substituent(s),

Q is CH or N, and

ℓ is an integer of 0 or 1,

and a pharmaceutically acceptable salt thereof.

2. A compound of claim 1, wherein

R^1 is hydrogen,

R^2 is hydrogen, lower alkyl, an acyl group, aryl, cyano or mono-(or di- or tri-)halo(lower)alkyl,

R^3 is hydrogen, lower alkyl, lower alkynyl, lower alkoxy, halogen, an acyl group, acyl(lower)alkyl, acyloxy(lower)alkyl, hydroxyimino(lower)alkyl which may have one or more suitable substituent(s), hydroxy(lower)alkyl which may have one or more suitable substituent(s), cyano(lower)alkyl, mono(or di-)lower alkoxy(lower)alkyl which may have one or more suitable substituent(s), lower alkyl substituted with aryl which may have one or more suitable substituent(s), mono-(or di-)lower alkylamino(lower)alkyl, hydrazino(lower)alkyl which may have one or more suitable substituent(s), mono-(or di-)lower alkoxy(lower)alkylamino(lower)alkyl,

N-(lower)alkylamino(lower)alkyl which may have one or more suitable substituent(s), lower alkyl substituted with heterocyclic group which may have one or more suitable substituent(s), heterocyclic group which may have one or more suitable substituent(s), heterocyclicthio, heterocyclicthio(lower)alkyl which may have one or more suitable substituent(s), heterocyclicoxy(lower)alkyl, aryl which may have one or more suitable substituent(s), amino, nitro, halo(lower)alkyl, hydroxy(lower)alkylimino(lower)alkyl, hydroxy(lower)alkylamino(lower)alkyl, bis-[hydroxy(lower)alkyl]amino(lower)alkyl, mercapto(lower)alkyl or amidinothio(lower)alkyl,

X is a group of the formula :

$-NHCO-$, $-NHSO_2-$, $-NHCOCO-$, $-NHCOCH=CH-$, $-NHCOCH_2-$, $-NHCONH-$ or $-N(R^5)-CO-$ (wherein R^5 is lower alkyl),

Y is heterocyclic group which may have one or more suitable substituent(s), or aryl which may have one or more suitable substituent(s), and

ℓ is an integer of 1.

3. A compound of claim 2, wherein

R^1 is hydrogen,

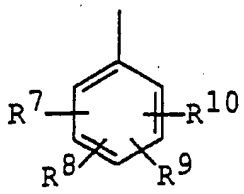
R^2 is lower alkyl or mono-(or di- or tri-)halo(lower)alkyl,

R^3 is hydroxy(lower)alkyl which may have one or more suitable substituent(s), lower alkyl substituted with heterocyclic group which may have one or more suitable substituent(s), acyl(lower)alkyl or heterocyclicthio(lower)alkyl,

X is a group of the formula :

$-NHCO-$,

Y is a group of the formula :

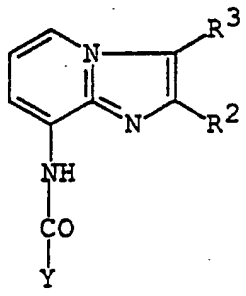


[wherein R^7, R^8, R^9 and R^{10} are each hydrogen, halogen or lower alkyl],

Q is CH, and

ℓ is an integer of 1.

4. A compound of claim 3, which is shown by the following formula :

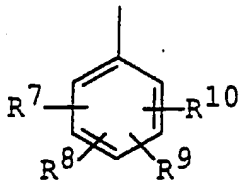


wherein

R^2 is tri-halo(lower)alkyl or lower alkyl,

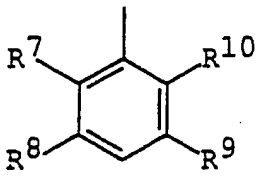
R^3 is hydroxy(lower)alkyl, lower alkyl substituted with unsaturated 5 or 6-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s), lower alkoxy(lower)alkylaminocarbonyl(lower)alkyl or heterocyclicthio(lower)alkyl (wherein heterocyclic group is unsaturated 5 or 6-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s)),

Y is a group of the formula :



[wherein R^7, R^8, R^9 and R^{10} are each hydrogen or halogen].

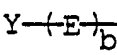
5. A compound of claim 4, wherein Y is a group of the formula :



(wherein R^7 is halogen,
R^8 is hydrogen,
R^9 is hydrogen,
R^{10} is halogen.

6. A process for preparing a compound of claim 1, or a salt thereof, which comprises

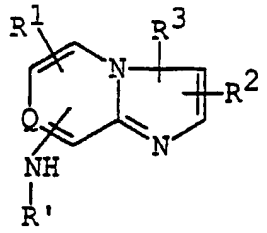
(i) reacting a compound of the formula :



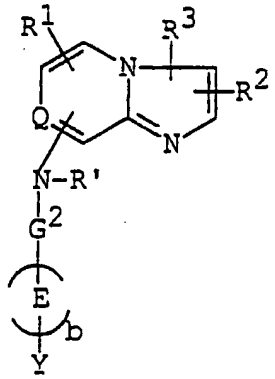
wherein Y is as defined in claim 1,
E is lower alkylene, lower alkenylene,

or a group of the formula :

(wherein G^1 is -COOH or $-SO_3H$, and
b is an integer of 0 or 1),
or its reactive derivative at the carboxy or sulfo group or a salt thereof, with a compound of the formula :



wherein R^1, R^2, R^3 and Q are each as defined in claim 1,
and
R' is hydrogen or lower alkyl,
or its reactive derivative at the amino group or a salt thereof, to give a compound of the formula :

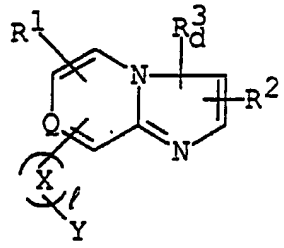


wherein R^1, R^2, R^3, Y, R', E, Q and b are each as defined above, and

G^2 is -CO- or $-SO_2-$,

or a salt thereof, or

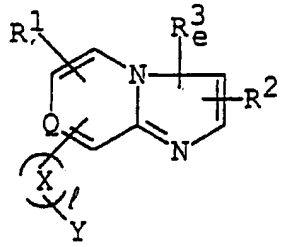
(ii) subjecting a compound of the formula :



wherein R^1, R^2, X, Y, Q and ℓ are each as defined in claim 1, and

R^3_d is hydrogen,

or a salt thereof, with lower alkane substituted with oxo to give a compound of the formula :



wherein R^1, R^2, X, Y, Q and ℓ are each as defined above, and

R^3_e is hydroxy(lower)alkyl,

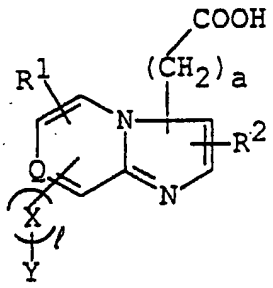
or a salt thereof, or

(iii) reacting a compound of the formula :

$$NH_2\text{-}R'''$$

wherein R"' is lower alkyl, cyclo(lower)alkyl, lower alkyl substituted with heterocyclic group which may have one or more suitable substituent(s), lower alkoxy(lower)alkyl, hydroxy(lower)alkyl, amino, heterocyclic group, carboxy(lower)alkyl, protected carboxy(lower)alkyl, lower alkyl substituted with aryl which may have one or more suitable substituent(s), arylsulfonyl or cyano(lower)alkyl,

or its reactive derivative at the amino group or a salt thereof, with a compound of the formula :

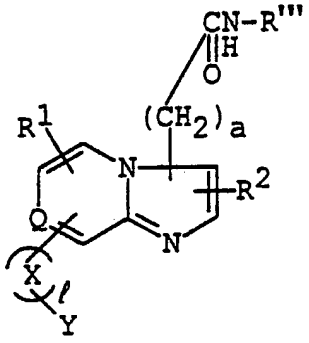


wherein R^1, R^2, X, Y, Q and ℓ are each as defined in claim 1, and

a is an integer of 0 to 6,

or its reactive derivative at the carboxy group,

or a salt thereof, to give a compound of the formula :



wherein R^1, R^2, R"', X, Y, Q, ℓ and a are each as defined above,

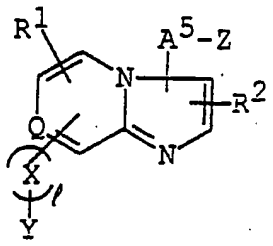
or a salt thereof, or

(iv) reacting a compound of the formula :

V - H

wherein V is heterocyclic group which may have one or more suitable substituent(s), heterocyclicthio, lower alkylamino which may have one or more suitable substituent(s), hydroxy(lower)alkylamino, bis-hydroxy(lower)alkylamino, amidinothio or tri-lower alkylphosphite,

with a compound of the formula :

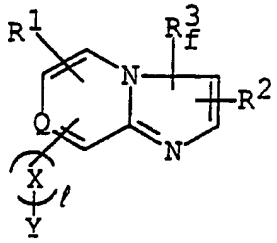


wherein R^1, R^2, X, Y, Q and ℓ are each as defined in claim 1,

Z is leaving group, and

A^5 is lower alkylene,

or a salt thereof, to give a compound of the formula :



wherein R^1, R^2, X, Y, Q and ℓ are each as defined above,

R_f^3 is lower alkyl substituted with heterocyclic group which may have one or more suitable substituent(s), heterocyclicthio(lower)-alkyl, lower alkylamino(lower)alkyl which may have one or more suitable

substituent(s), hydroxy(lower)alkylamino-(lower)alkyl, bis-[hydroxy(lower)alkyl]-amino(lower)alkyl, amidinothio(lower)-alkyl or di-(lower)alkoxyphosphoryl-(lower)alkyl,

or a salt thereof.

7. A pharmaceutical composition which comprises, as an active ingredient, a compound of claim 1 or a pharmaceutically acceptable salt thereof in admixture with pharmaceutically acceptable carriers or excipients.

8. Use of a compound of claim 1 or a pharmaceutically acceptable salt thereof for the manufacture of a medicament.

9. A compound of claim 1 or a pharmaceutically acceptable salt thereof for use as a medicament.

10. A method for the prophylactic and/or the therapeutic treatment of diseases caused by abnormal bone metabolism which comprises administering a compound of claim 1 or a pharmaceutically acceptable salt thereof to a human being or an animal.

INTERNATIONAL SEARCH REPORT

Int ional Application No
PCT/JP 96/01103

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D471/04 C07D487/04 A61K31/435 A61K31/495
//(C07D471/04,235:00,221:00),(C07D487/04,241:00,235:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO,A,89 03833 (HÄSSLE) 5 May 1989 whole document ---	1,7
X	EP,A,0 634 169 (TAKEDA) 18 January 1995 see claim 1; example 120 --- -/--	1,7

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date -

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 July 1996	24.07.96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Alfaro Faus, I

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 114, no. 25, 1991 Columbus, Ohio, US; abstract no. 247280r, SHIOKAWA ET AL.: "8-Aroylamino-3-alkynyl-2-alkylimidazo[1,2-a]pyridines as ulcer inhibitors" page 764; XP002008623 see abstract and 12th Collective Index, page 7420, column 3, lines 5-28 and p. 7500, c. 2, 83-86 & JP,A,00 331 280 (FUJISAWA) 12 February 1991	1,7
X	JOURNAL OF MEDICINAL CHEMISTRY, vol. 30, 1987, WASHINGTON US, pages 2031-2046, XP002008621 J.J. KAMINSKI ET AL.: "Antiulcer Agents. 2. Gastric antisecretory,cytoprotective and metabolic properties of substituted imidazo[1,2-a]pyridines and analogues" see tables III,VI	1,7
X	JOURNAL OF MEDICINAL CHEMISTRY, vol. 32, 1989, WASHINGTON US, pages 1686-1700, XP002008622 J.J. KAMINSKI ET AL.: "Antiulcer agents. 4. Conformational considerations and the antiulcer activity of substituted imidazo[1,2-a]pyridines and related analogues" see tables I,II	1,7
X	EP,A,0 596 406 (FUJISAWA) 11 May 1994 see claims 1,8	1,7
X	WO,A,95 07276 (EISAI) 16 March 1995 see claims 1,13; example 20 & EP,A,0 673 937 (EISAI) 27 September 1995	1,7

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP 96/01103

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 10 is directed to a method of treatment of (diagnostic method practised on) the human/animal body the search has been carried out and based on the alleged effects of the compound/composition.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

On grounds of Articles 6 and 17.2a (ii) of the PCT and of the Guidelines for examination of the EPO, Part B, Chapter III, 2.2 (economic reasons) the search of the compounds of formule I is incomplete.

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Int ional Application No
PCT/JP 96/01103

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-8903833	05-05-89	AU-B-	2620388	23-05-89
		EP-A-	0339071	02-11-89
		JP-T-	2501929	28-06-90
EP-A-634169	18-01-95	CA-A-	2126966	30-12-94
		JP-A-	7069890	14-03-95
EP-A-596406	11-05-94	AU-B-	5024293	12-05-94
		CA-A-	2102137	03-05-94
		CN-A-	1089947	27-07-94
		HU-A-	66302	28-11-94
		JP-A-	7300478	14-11-95
		ZA-A-	9308011	09-06-94
WO-A-9507276	16-03-95	AU-B-	7623794	27-03-95
		CA-A-	2146961	16-03-95
		CN-A-	1114506	03-01-96
		EP-A-	0673937	27-09-95
		FI-A-	952272	06-07-95
		HU-A-	71551	28-12-95
		JP-A-	7165708	27-06-95
		NO-A-	951813	09-05-95